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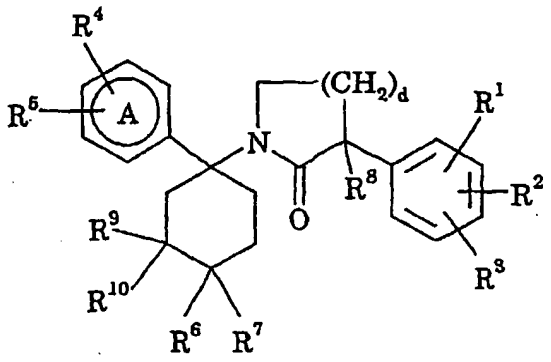
(54) Title: GEM-DISUBSTITUTED CYCLOHEXANE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS



(I)

(57) Abstract: The present invention relates compounds of the formula (I): wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9 and R^{10} represent a variety of substituents; ring A is a phenyl or pyridyl ring; d is zero, 1 or 2; and pharmaceutically acceptable salts and N-oxides thereof. The compounds are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia.

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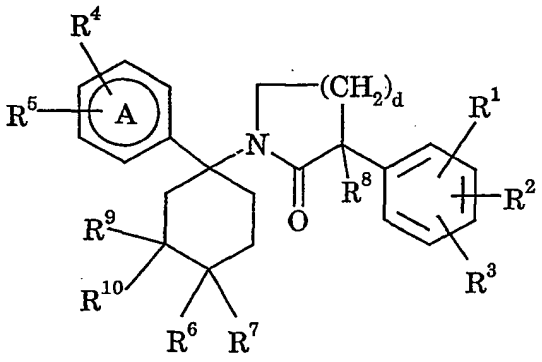
GEM-DISUBSTITUTED CYCLOHEXANE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

This invention relates to a class of gem-disubstituted cyclohexane derivatives which are useful as tachykinin antagonists. More particularly, the compounds of the invention are useful as neurokinin 1 (NK-1) receptor antagonists.

The present invention provides compounds of the formula (I):



(I)

wherein

ring A is a phenyl or pyridyl ring;

R^1 represents hydroxy, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-4}alkyl, C_{1-6}alkoxyC_{1-4}alkoxy, fluoroC_{1-6}alkoxyC_{1-4}alkyl, C_{2-6}alkenyloxy, C_{3-7}cycloalkoxy, C_{3-7}cycloalkylC_{1-4}alkoxy, phenoxy, cyano, halogen, NR^aR^b, SR^a, SOR^a, SO_2R^a, OSO_2R^a, NR^aCOR^c, COR^a, CO_2R^a or $CONR^aR^b$ where R^a and R^b each independently represent hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, fluoroC_{1-4}alkyl or $CH_2CO_2C_{1-4}$alkyl, and R^c represents C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl or phenyl;

R^2 represents hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

or when R^2 is adjacent to R^1, they may be joined together such that there is formed a 5- or 6-membered saturated or unsaturated ring containing one or two atoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by a group selected from C_{1-4}alkyl, CF_3, =O or =S;

R^3 represents hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, cyano, SR^a, SOR^a, SO_2R^a, NR^aR^b, NR^aCOR^c, COR^a, CO_2R^a, $CONR^aR^b$ or C_{1-4}alkyl substituted by cyano, CO_2R^a or $CONR^aR^b$ where R^a, R^b and R^c are as previously defined;

or R^3 represents a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms, selected from nitrogen, oxygen and sulphur, which group is optionally substituted by one or two groups selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, trifluoromethyl, OCF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, phenyl, $-(CH_2)_rNR^aR^b$, $-(CH_2)_rNR^aCOR^b$, $-(CH_2)_rCONR^aR^b$, or $CH_2C(O)R^a$, where R^a and R^b are as previously defined and r is zero, 1 or 2;

R^4 represents hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, hydroxy, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b are as previously defined;

R^5 represents hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl or C_{1-6}alkoxy substituted by C_{1-4}alkoxy;

R^6 represents hydrogen, hydroxy or a C_{1-4}alkyl group optionally substituted by a hydroxy group;

R^7 represents hydrogen, hydroxy, $-(CH_2)_nNR^{11}R^{12}$, $-(CH_2)_nCO_2R^a$, carbocyclyl, C-linked heterocyclyl or heteroaryl, where R^a is as previously defined;

or R^6 and R^7 together represent =O, $=CHCO_2R^a$ or $-O(CH_2)_mO-$, where R^a is as previously defined;

R^8 represents hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkyl substituted by C_{1-4}alkoxy or C_{1-6}alkoxy substituted by C_{1-4}alkoxy;

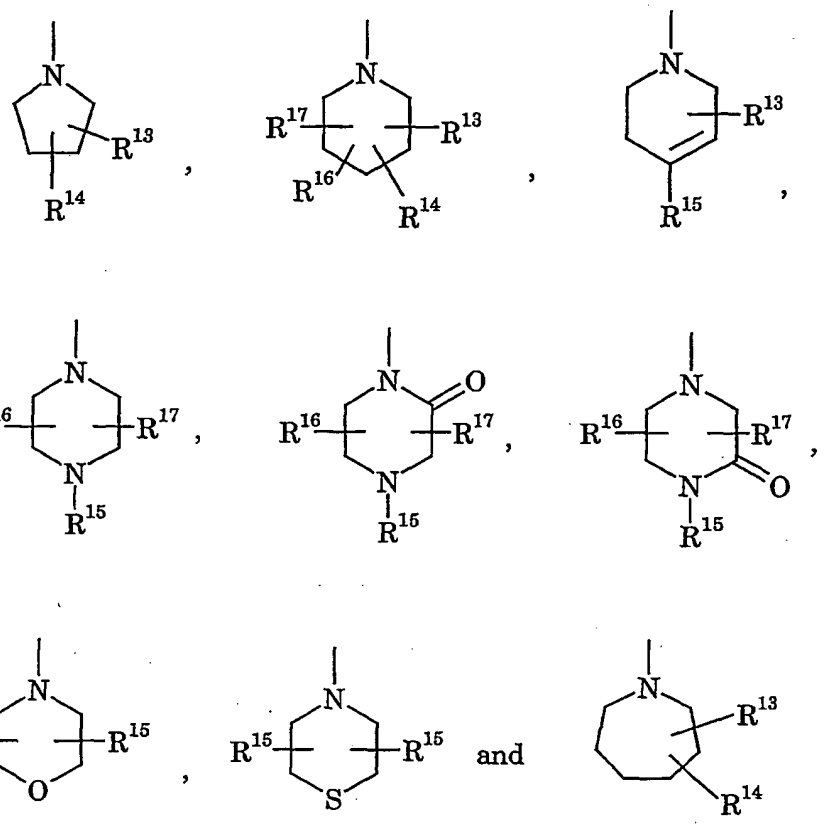
R^9 represents hydrogen, halogen or hydroxy and R^{10} represents hydrogen;

or R^9 and R^{10} both represent fluorine or together represent oxo (=O);

R^{11} and R^{12} each independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl, $CO_2(CH_2)_pNR^aR^b$, $(CH_2)_pNR^aCOR^b$, $(CH_2)_pNR^aCO_2R^b$,

$(CH_2)_qCONR^aaryl$ or $(CH_2)_qCONR^aheterocyclyl$ where R^a and R^b are as previously defined;

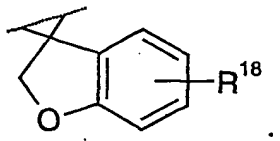
or R^{11} and R^{12}, together with the nitrogen atom to which they are attached, represent a ring selected from the group consisting of:



R^{13} and R^{14} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, (C_{2-6}alkenyl)aryl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$heterocyclyl, $(CH_2)_qNR^aR^b$, $O(CH_2)_qC_{3-7}$cycloalkyl, $O(CH_2)_q$aryl, $O(CH_2)_q$heterocyclyl, $O(CH_2)_pNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, when they are attached to the same carbon atom, R^{13} and R^{14} may together represent =O, $=CHCO_2R^a$, $-O(CH_2)_mO-$, $-CH_2O(CH_2)_s-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OCH_2C(CH_3)_2-$, $-CH_2OC(CH_3)_2CH_2-$,

$-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-OC(O)CH_2CH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-C(O)OCH_2C(CH_3)_2-$, $-OCH_2(CH_2)_s-$, $-OC(CH_3)_2CH_2CH_2-$, $-OCH_2C(CH_3)_2CH_2-$, $-OCH_2CH_2C(CH_3)_2-$, $-OCH_2CH=CHCH_2-$, $-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$, $-OCH_2CH_2C(O)CH_2-$, or a group of the formula



;

or, where they are attached to adjacent carbon atoms, R^{13} and R^{14} may together represent $-OCH_2CH_2-$ or $-OCH_2CH(OH)-$, or R^{13} and R^{14} may together form a fused benzene ring;

or, R^{13} and R^{14} together form a C_{1-2}alkylene bridge across the pyrrolidine, piperidine or hexamethyleneimine ring to which they are attached;

R^{15} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, where they are attached to adjacent carbon atoms, R^{15} and R^{16} may together form a fused imidazolyl or triazolyl ring;

R^{16} and R^{17} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl or oxo (=O);

R^{18} represents hydrogen, halogen, hydroxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or fluoroC_{1-4}alkyl;

d is zero, 1, 2 or 3;

n is zero, 1 or 2;

m is 1 or 2;

p is 1, 2, 3 or 4;

q is zero, 1, 2, 3 or 4; and

s is 1, 2 or 3;

and pharmaceutically acceptable salts and N-oxides thereof.

A preferred class of compound of formula (I) is that wherein R^1 is hydroxy, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{3-7}cycloalkoxy, C_{3-7}cycloalkylC_{1-4}alkoxy, cyano, NR^aR^b, SR^a, OSO_2R^a, or R^1 together with the group R^2 form a 5-membered saturated ring containing one oxygen atom.

A particularly preferred class of compound of formula (I) is that wherein R^1 is C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{3-7}cycloalkoxy or C_{3-7}cycloalkoxyC_{1-4}alkyl, especially methyl, trifluoromethyl, methoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, cyclopropoxy or cyclopropylmethoxy.

Another preferred class of compound of formula (I) is that wherein R^2 is a hydrogen, fluorine or chlorine atom, especially a hydrogen atom.

A further preferred class of compound of formula (I) is that wherein R^3 is hydrogen, halogen, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, cyano, NR^aR^b, NR^aCOR^d (where R^d is methyl, methoxy, trifluoromethyl or phenyl), or a 5-membered aromatic heterocyclic group as previously defined.

Also preferred is the class of compounds of formula (I) in which R^3 is C_{1-6}alkyl, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy or a 5-membered aromatic heterocyclic group as previously defined, especially methyl, trifluoromethyl, trifluoromethoxy or 5-trifluoromethyl-1,2,3,4-tetrazol-1-yl.

Preferably R^1 and R^3 are in the 3 and 5 positions of the phenyl ring.

More preferably R^1 is 3-fluoro or 3-CF_3.

More preferably R^3 is 5-fluoro or 5-CF_3.

More preferably R^2 is hydrogen.

Most preferably R^1 is 3-CF_3, R^2 is hydrogen and R^3 is 5-CF_3.

Another preferred class of compounds of formula (I) is that wherein R^1 and R^3 are in the 2- and 5-positions of the phenyl ring.

In this sub-class of compounds of formula (I), R^1 is preferably C_{1-6}alkoxy or C_{3-7}cycloalkoxy, especially methoxy or cyclopropoxy.

Also in this sub-class of compounds of formula (I), R^2 is preferably hydrogen.

Also, in this sub-class of compounds of formula (I) R^3 is preferably hydrogen, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy or a 5-membered aromatic heterocyclic

group as previously defined. Most especially, R^3 is hydrogen, methoxy or trifluoromethoxy.

A further preferred class of compound of formula (I) is that wherein R^4 is hydrogen.

Another preferred class of compounds of formula (I) is that wherein R^5 is hydrogen, fluorine, chlorine or CF_3, especially hydrogen or fluorine.

Preferably R^4 is hydrogen and R^5 is hydrogen or 4-fluoro.

Another further preferred class of compounds of formula (I) is that wherein R^6 is hydrogen.

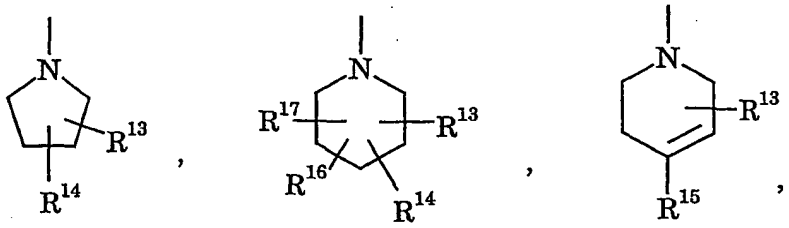
Another preferred class of compounds of formula (I) is that in which R^9 and R^{10} each represents hydrogen.

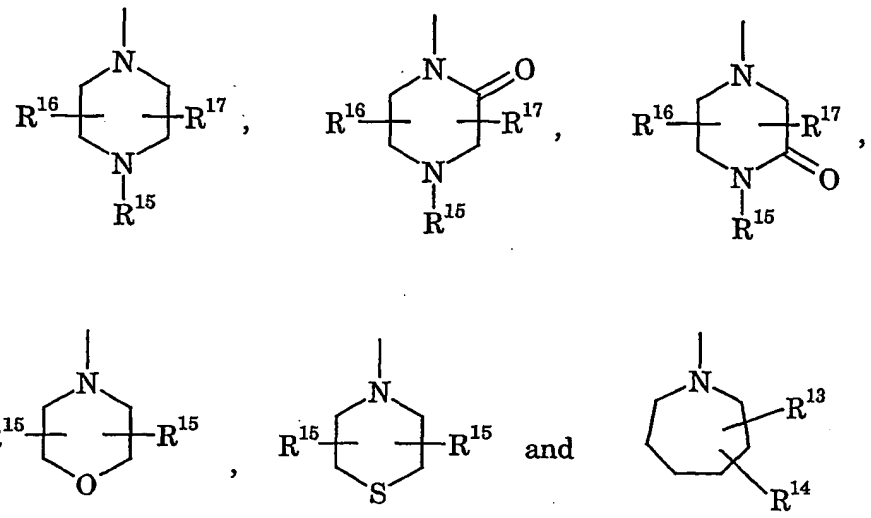
A further preferred class of compounds of formula (I) is that wherein R^7 is $-(CH_2)_nNR^{11}R^{12}$ or wherein R^6 and R^7 together represent =O or $-O(CH_2)_mO-$ wherein m is as previously defined.

A further preferred class of compounds of formula (I) is that wherein R^{11} represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $(CH_2)_pNR^aCO_2R^b$ or $(CH_2)_qCONR^a$aryl;

and R^{12} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl or CO_2C_{1-6}alkyl;

or R^{11} and R^{12} together with the nitrogen atom to which they are attached represent a ring selected from the group consisting of

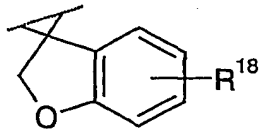




A further preferred class of compounds of formula (I) is that wherein R^{13} represents hydrogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $(CH_2)_qNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H or CO_2C_{1-6}alkyl;

and R^{14} represents hydrogen, halogen, hydroxy, C_{1-6}alkyl or $(CH_2)_q NR^aR^b$;

or when they are attached to the same carbon atom, R^{13} and R^{14} may together represent =O, $-O(CH_2)_mO-$, $-CH_2O(CH_2)_s-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OCH_2C(CH_3)_2-$, $-CH_2OC(CH_3)_2CH_2-$, $-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-OC(O)CH_2CH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-C(O)OCH_2C(CH_3)_2-$, $-OCH_2(CH_2)_s-$, $-OC(CH_3)_2CH_2CH_2-$, $-OCH_2CH=CHCH_2-$, $-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$, or a group of the formula



;

or, when they are attached to adjacent carbon atoms, R^{13} and R^{14} may together represent $-OCH_2CH_2-$ or $-OCH_2CH(OH)-$, or R^{13} and R^{14} may together form a fused benzene ring;

or R^{13} and R^{14} together form a C_{1-2}alkylene bridge across the pyrrolidine or piperidine ring to which they are attached.

A further preferred class of compounds of formula (I) is that wherein R^{15} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl,

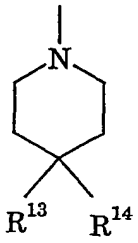
$(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)C_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl or CO_2C_{1-6}alkyl.

A yet further preferred class of compounds of formula (I) is that wherein R^{12} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl or CO_2C_{1-6}alkyl.

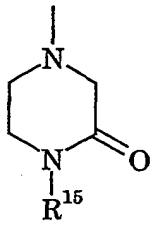
A particularly preferred class of compounds of formula (I) is that wherein R^{11} represents C_{1-6}alkyl (especially methyl);

and R^{12} represents C_{1-6}alkyl (especially methyl);

or R^{11} and R^{12} together with the nitrogen atom to which they are attached represent a ring selected from the group consisting of:



and



A further particularly preferred class of compounds of formula (I) is that wherein R^{13} and R^{14} together represent =O, $-OCH_2CH_2O-$, $-OCH_2CH_2CH_2-$ or $-CH_2OCH_2CH_2-$.

A yet further particularly preferred class of compounds of formula (I) is that wherein R^{15} represents phenyl.

Another preferred class of compound of formula (I) is that wherein the ring A is a phenyl ring.

A still further preferred class of compounds of formula (I) is that wherein d represents 1 or 2.

Also preferred are those compounds of formula (I) in which R^8 represents hydrogen, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy, and most especially hydrogen, hydroxy, methyl or methoxy.

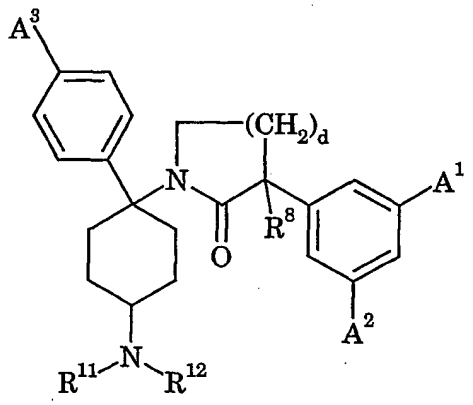
Another preferred class of compounds of formula (I) is that wherein n is zero.

A further preferred class of compounds of formula (I) is that wherein m is 2.

Another preferred class of compounds of formula (I) is that wherein p is 1, 2 or 3, particularly 1 or 2, and especially 1.

A further preferred class of compounds of formula (I) is that wherein q is zero, 1 or 2, particularly zero or 1.

One favoured group of compounds of the present invention are of the formula (Ia) and pharmaceutically acceptable salts and N-oxides thereof:



(Ia)

wherein

A^1 is fluorine or CF_3;

A^2 is fluorine or CF_3;

A^3 is fluorine or hydrogen;

d is 1 or 2; and

R^8, R^{11} and R^{12} are as defined in relation to formula (I).

When any variable occurs more than one time in formula (I) or formula (Ia) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

As used herein, the term "hydroxyC_{1-6}alkyl" means a C_{1-6}alkyl group in which one or more (in particular 1 to 3, and especially 1) hydrogen atoms have

been replaced by hydroxy groups. Particularly preferred are hydroxyC_{1-3}alkyl groups, for example, CH_2OH, CH_2CH_2OH, $CH(CH_3)OH$ or $C(CH_3)_2OH$, and most especially CH_2OH.

As used herein, the terms "fluoroC_{1-6}alkyl" and fluoroC_{1-6}alkoxy" means a C_{1-6}alkyl or C_{1-6}alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by fluorine atoms. Particularly preferred are fluoroC_{1-3}alkyl and fluoroC_{1-3}alkoxy groups, for example, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, OCF_3, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially CF_3, OCF_3 and OCH_2CF_3.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable $(CH_2)_qC_{3-7}$cycloalkyl group where q is 1 may be, for example, cyclopropylmethyl or cyclohexylmethyl.

Similarly cycloalkoxy groups referred to herein may represent, for example, cyclopropoxy or cyclobutoxy.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is acetylene or propargyl.

When used herein the term "halogen" means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred, unless otherwise stated.

As used herein, the term "aryl" as a group or part of a group means an aromatic radical such as phenyl, biphenyl or naphthyl, wherein said phenyl, biphenyl or naphthyl group may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl or $-O(CH_2)_mO-$. Preferably said phenyl, biphenyl or naphthyl group is optionally substituted by one or two substituents, especially none or one. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl, trifluormethoxy or vinyl.

As used herein, the term "heterocyclyl" as a group or part of a group means a saturated, partially saturated or unsaturated heteroatom-containing ring-shaped radical, where the heteroatoms may be selected from nitrogen,

oxygen and sulfur. Examples of saturated heterocyclyl radicals include N-linked saturated 3 to 6-membered heteromonocyclic groups containing 1 to 3 nitrogen atoms and optionally 1 oxygen or sulfur atom (for example, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl or piperazinyl substituted on the nitrogen atom by a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by hydroxy or C_{1-2}alkoxy). Examples of saturated heterocyclyl radicals also include C-linked saturated 3 to 6-membered heteromonocyclic groups containing, for example, one oxygen atom (for instance, tetrahydrofuranyl or tetrahydropyranyl). Examples of partially saturated heterocyclyl radicals include N-linked partially saturated 3 to 6-membered heteromonocyclic groups containing 1 to 3 nitrogen atoms (for example, 3-pyrroline). Examples of unsaturated heterocyclyl radicals include heteroaromatic rings selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, oxadiazolyl, thiadiazolyl, triazinyl, tetrazolyl, indolyl, benzofuranyl, benzthiophenyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzthiazolyl or benzisothiazolyl.

Said saturated and partially saturated heterocyclyl radicals may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, oxo (=O), NR^aR^b, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl, $-O(CH_2)_mO-$, $-OCH_2CH_2CH_2-$, $-CH_2OCH_2CH_2-$ or $-CH_2OCH_2C(O)-$. Preferably said saturated or partially saturated heterocyclyl radical is optionally substituted by one or two substituents, especially none or one. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl, trifluoromethoxy, oxo, vinyl, C_{1-4}alkylamino (especially methylamino) or di(C_{1-4}alkyl)amino (especially dimethylamino).

Said unsaturated heterocyclyl radicals may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, NR^aR^b, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl or $-O(CH_2)_mO-$. Preferably said unsaturated heterocyclyl is optionally substituted by one or two substituents, especially none or one. Particularly preferred

substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl, trifluoromethoxy or vinyl.

As used herein, the term "carbocyclyl" as a group or part of a group means a 3 to 7-membered cycloalkyl radical such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein said cycloalkyl radical may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl or $-O(CH_2)_mO-$. Preferably said cycloalkyl radical is substituted by one or two substituents, especially one. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), methoxy, hydroxyC_{1-4}alkyl (especially $C(CH_3)_2OH$), trifluoromethyl, trifluoromethoxy or vinyl.

Specific compounds within the scope of this invention include:

(*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-piperidinone;

(*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone;

(*RS*)-3-hydroxy-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone;

(*RS*)-3-methyl-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro-[4.5]decan-8-yl)-2-pyrrolidinone;

(*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-piperidinone;

(*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-pyrrolidinone;

(*RS*)-3-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-pyrrolidinone;

(*RS*)-3-methyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone;

cis-(*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone;

trans-(*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone;

trans-(*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-dimethylamino-1-phenylcyclohexyl)-2-pyrrolidinone;
trans-(*RS*)-3-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone;
trans-(*RS*)-3-methoxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone; and
trans-(*RS*)-3-methyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone;
and pharmaceutically acceptable salts and N-oxides thereof.

In a further aspect of the present invention, the compounds of formula (I) may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional

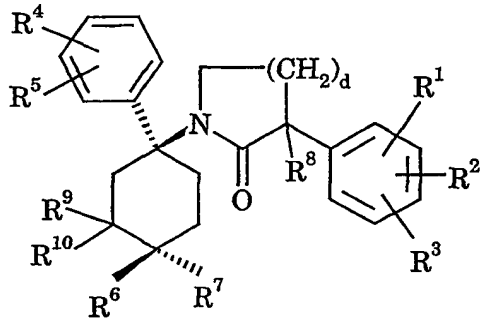
derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have one or more asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I) and (Ia) will have the stereochemistry of the 1- and 4-positions as shown in formula (Ib)



(Ib)

It will be appreciated that the preferred definitions of the various substituents recited herein may be taken alone or in combination and, unless otherwise stated, apply to the generic formula for compounds of the present

invention as well as to the preferred classes of compound represented by formula (Ia) and formula (Ib).

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers are particularly preferred.

A more detailed description of pharmaceutical compositions that are suitable for the formulation of compounds of the present invention is disclosed in US patent No. 6,071,927, the content of which is incorporated herein by reference (see in particular, column 8, line 50 to column 10, line 4).

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. A comprehensive listing of clinical conditions, uses and methods of treatment for which the compounds of the present invention will be useful is disclosed in US patent No. 6,071,927, the content of which is incorporated herein by reference (see, in particular, column 10, line 14 to column 22, line 18).

In particular, the compounds of the present invention are useful in the treatment of a variety of psychiatric disorders or disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; and anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including

post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders.

The compounds of the present invention are also particularly useful in the treatment of nociception and pain. Diseases and conditions in which pain predominates include soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, migraine, episiotomy pain, and burns.

The compounds of the present invention are also particularly useful in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; in the treatment of inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; and in the treatment of allergic disorders such as eczema and rhinitis.

The compounds of the present invention are also particularly useful in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as ulcerative colitis, Crohn's disease and irritable bowel syndrome.

The compounds of the present invention are also particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents, including those routinely used in cancer chemotherapy; by radiation including radiation therapy such as in the treatment of cancer; and in the treatment of post-operative nausea and vomiting.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in

particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

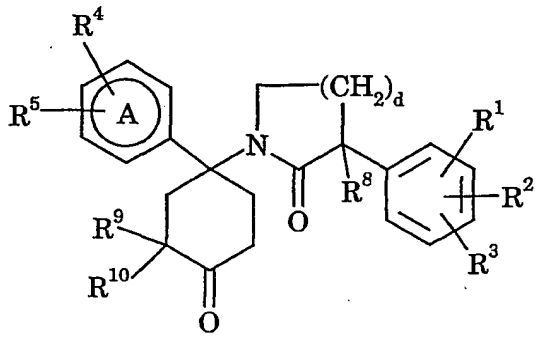
For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of psychiatric disorders, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), compounds of formula (I) in which R^6 is hydrogen and R^7 is a group of the formula $NR^{11}R^{12}$, may be prepared by the interconversion of a compound of formula (I) in which R^6 and R^7 together represent =O, hereinafter a compound of formula (II)



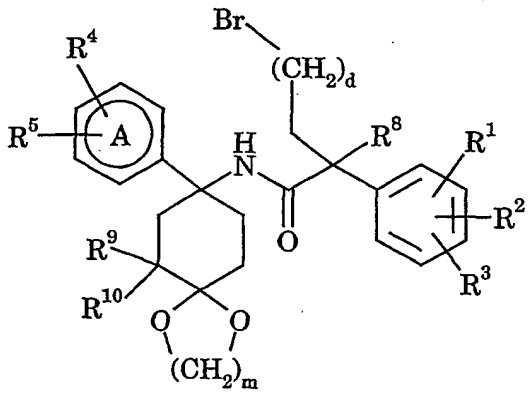
(II)

in which R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, ring A and d are as defined above, by reaction with an amine of the formula $HNR^{11}R^{12}$ in the presence of a reducing agent.

Suitable reducing agents of use in this reaction include, for example, sodium cyanoborohydride and sodium triacetoxyborohydride. The reaction may also be carried out in the presence of a Lewis acid such as zinc chloride.

The reaction is conveniently effected in a suitable solvent such as an alcohol, for example, methanol, or a halogenated hydrocarbon, for example, 1,2-dichloroethane, or a mixture thereof, at a temperature between 0°C and 50°C, conveniently at about room temperature.

According to another general process (B), compounds of formula (I) in which R^6 and R^7 together form a group $-O(CH_2)_mO-$, wherein m is as defined above, may be prepared by cyclising a compound of formula (III):



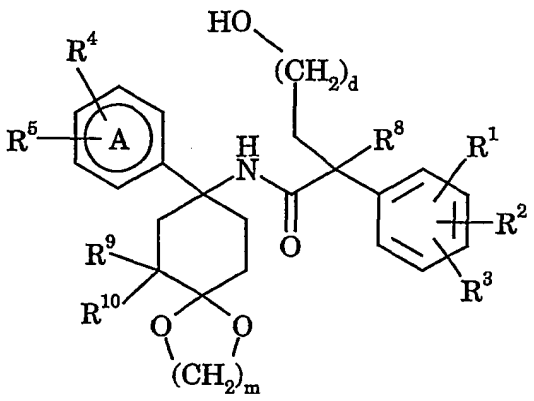
(III)

in which R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, ring A, d and m are as defined above.

The reaction is typically carried out in the presence of an inorganic base, such as sodium hexamethyldisilazide or sodium hydride, and in a solvent, such as an ether, for example tetrahydrofuran.

The resulting compound of formula (I) may be subjected to interconversion reactions to prepare further compounds of formula (I) in which R^6 and R^7 are as defined above.

In an alternative general process (C), compounds of formula (I) in which R^6 and R^7 together form a group $-O(CH_2)_mO-$, wherein m is as defined above, may be prepared by cyclising a compound of formula (IV):



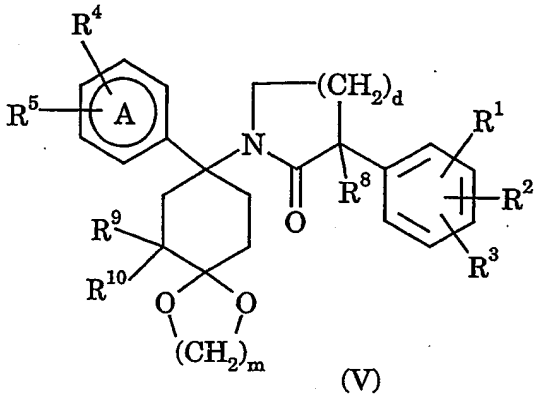
(IV)

in which R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, ring A, d and m are as defined above.

The reaction is typically carried out in the presence of a mesylating agent, such as methylsulphonyl chloride, an organic base, such as sodium hexamethyldisilylazide and in a solvent, such as an ether, for example tetrahydrofuran.

The resulting compound of formula (I), may be subjected to interconversion reactions to prepare further compounds of formula (I) in which R^6 and R^7 are as defined above.

According to another general process (D), compounds of formula (I) in which R^6 and R^7 together represent =O, i.e. compounds of formula (II) may be prepared by the interconversion of a compound of formula (I) in which R^6 and R^7 together form a group $-O(CH_2)_mO-$, wherein m is as defined above, hereinafter referred to as a compound of formula (V)



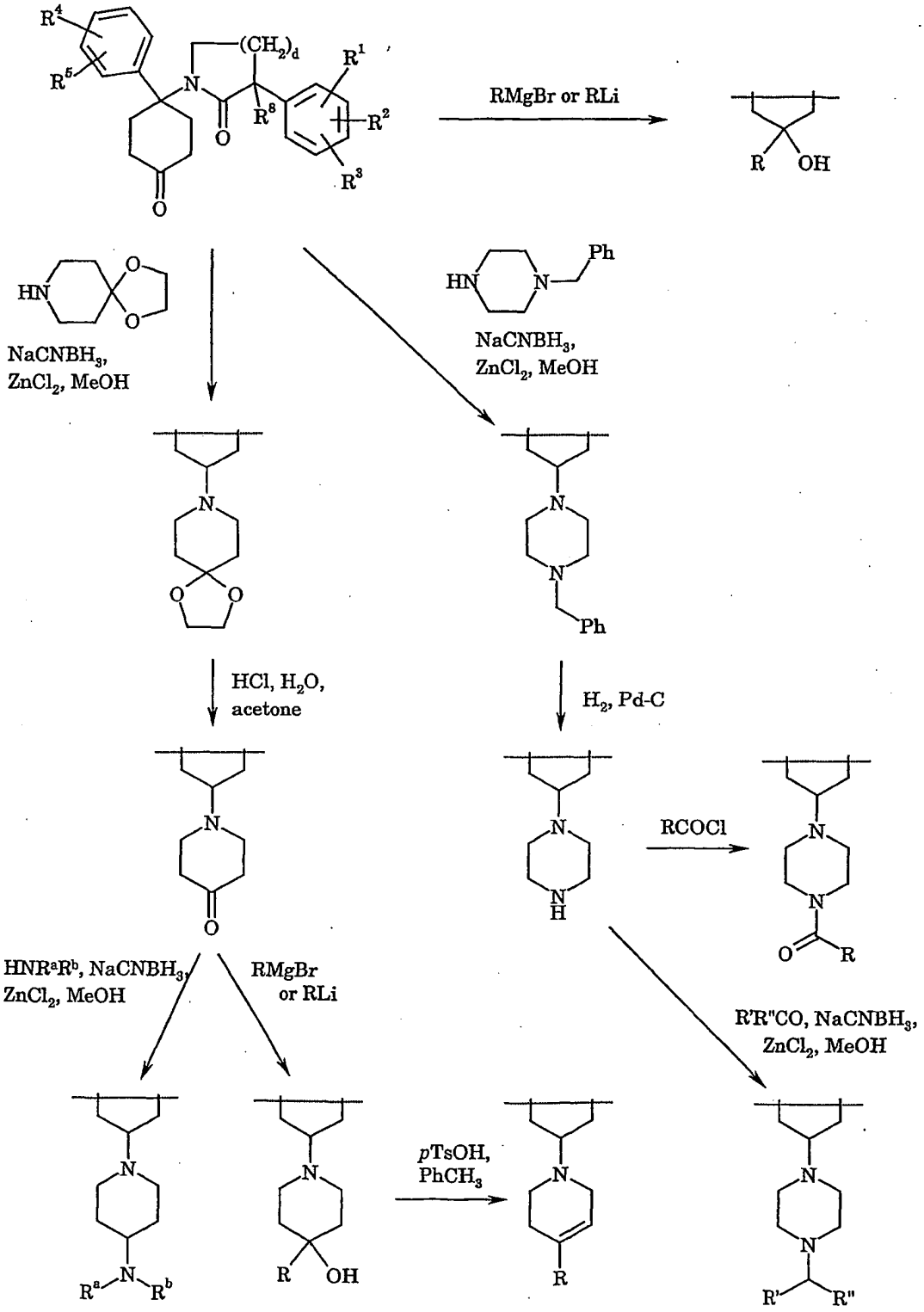
(V)

in which R^1, R^2, R^3, R^4, R^5, R^8, R^9, R^{10}, ring A, d and m are as defined above.

The reaction is typically effected in the presence of a mineral acid such as hydrochloric acid in a suitable solvent such as acetone at a temperature between room temperature and 70°C, for example, at about 50°C.

Interconversion reactions to modify the substituent R^7 may be effected using conventional procedures, for example as shown in the following Scheme 1. The methods depicted in Scheme 1 are not exhaustive and illustrate just some of the possible routes to further compounds of formula (I) (for convenience, only the bottom part of the formulae is drawn).

Scheme 1


RMgBr or RLi
NaCNBH3, ZnCl2, MeOH
NaCNBH3, ZnCl2, MeOH
HCl, H2O, acetone
H2, Pd-C
RCOCl
HNRaRb, NaCNBH3, ZnCl2, MeOH
RMgBr or RLi
pTsOH, PhCH3
R'R"CO, NaCNBH3, ZnCl2, MeOH

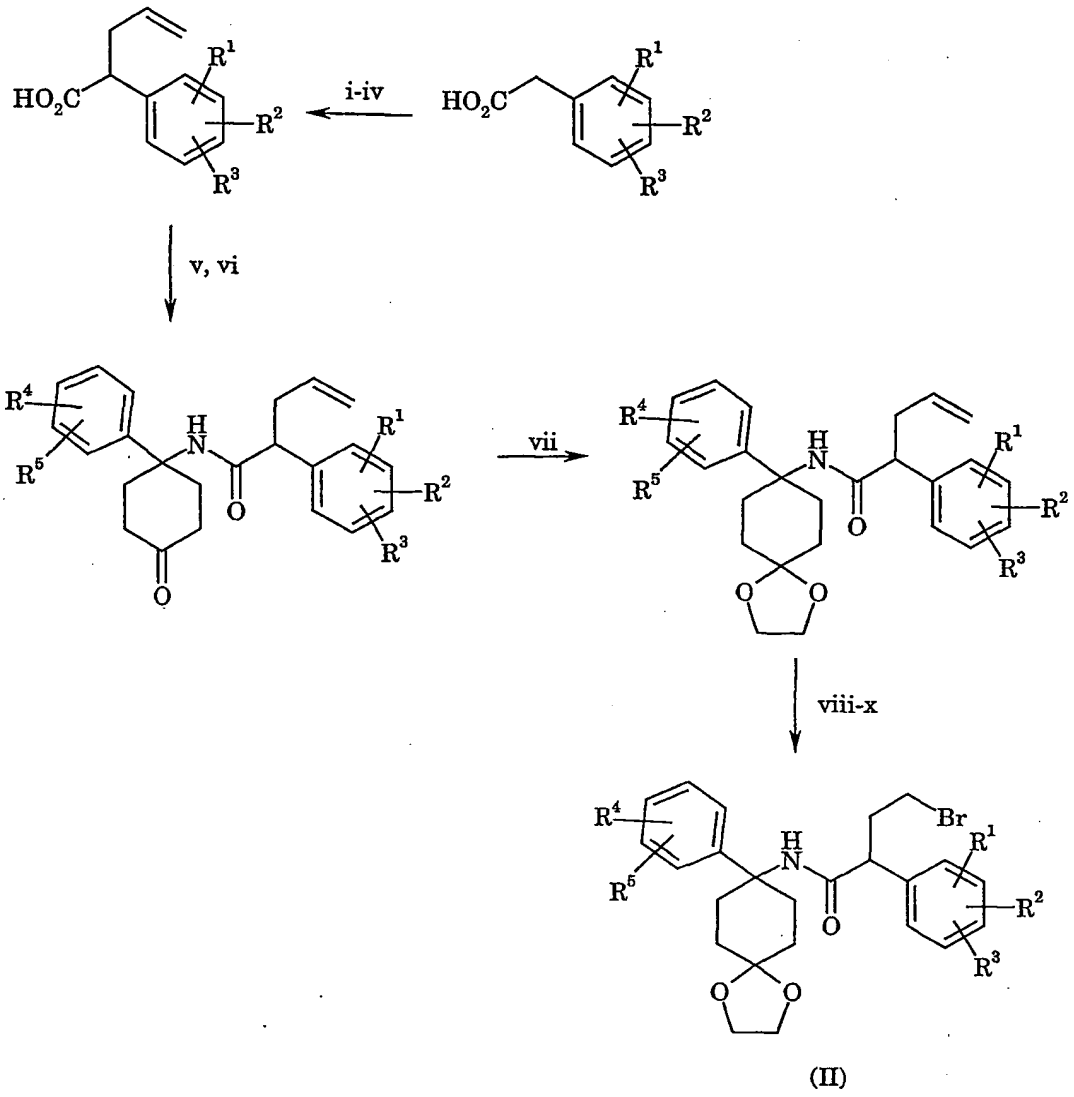
In the above Scheme 1, the groups designated as R, R' and R" take on any of the definitions of R^{13}, R^{14} or R^{15}, where appropriate.

Substituent groups R^9 and R^{10} may be added to the intermediates involved in production of the compounds of formula (I) in the later stages of the reaction procedures. Such addition may take place using conventional reagents and conditions.

Further details of suitable procedures for the preparation of compounds of formula (I) will be found in the accompanying Examples.

Compounds of formula (III) and (IV) may be prepared by a variety of methods well known to those skilled in the art. An example of suitable routes to the compounds of formula (III) is shown in the following Schemes 2 and 3, and to the compounds of formula (IV) in Scheme 4.

Scheme 2

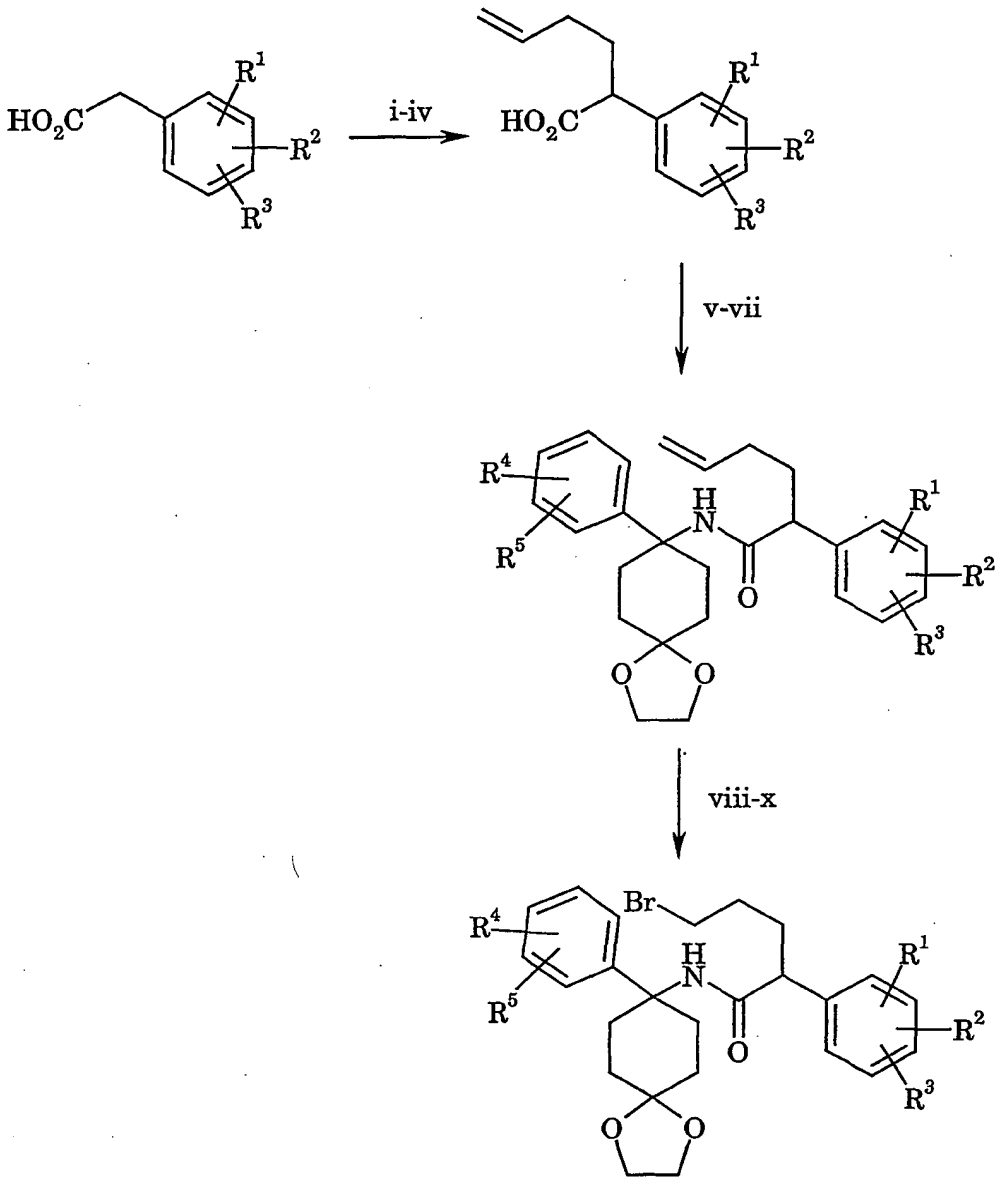


(II)

Appropriate reagents for each of the steps (i) to (x) in Scheme 2 may be as follows:

(i)	nBuLi;	(vi)	4-oxo-1-phenylcyclohexylamine, Py;
(ii)	$BrCH_2CH=CH_2$;	(vii)	$HOCH_2CH_2OH$, pTsOH, $PhCH_3$;
(iii)	dicyclohexylamine, Py;	(viii)	O_3;
(iv)	citric acid, EtOAc, H_2O;	(ix)	$NaBH_4$; and
(v)	$(COCl)_2$, DMF, CH_2Cl_2;	(x)	CBr_4, Ph_3P, Py.

Scheme 3

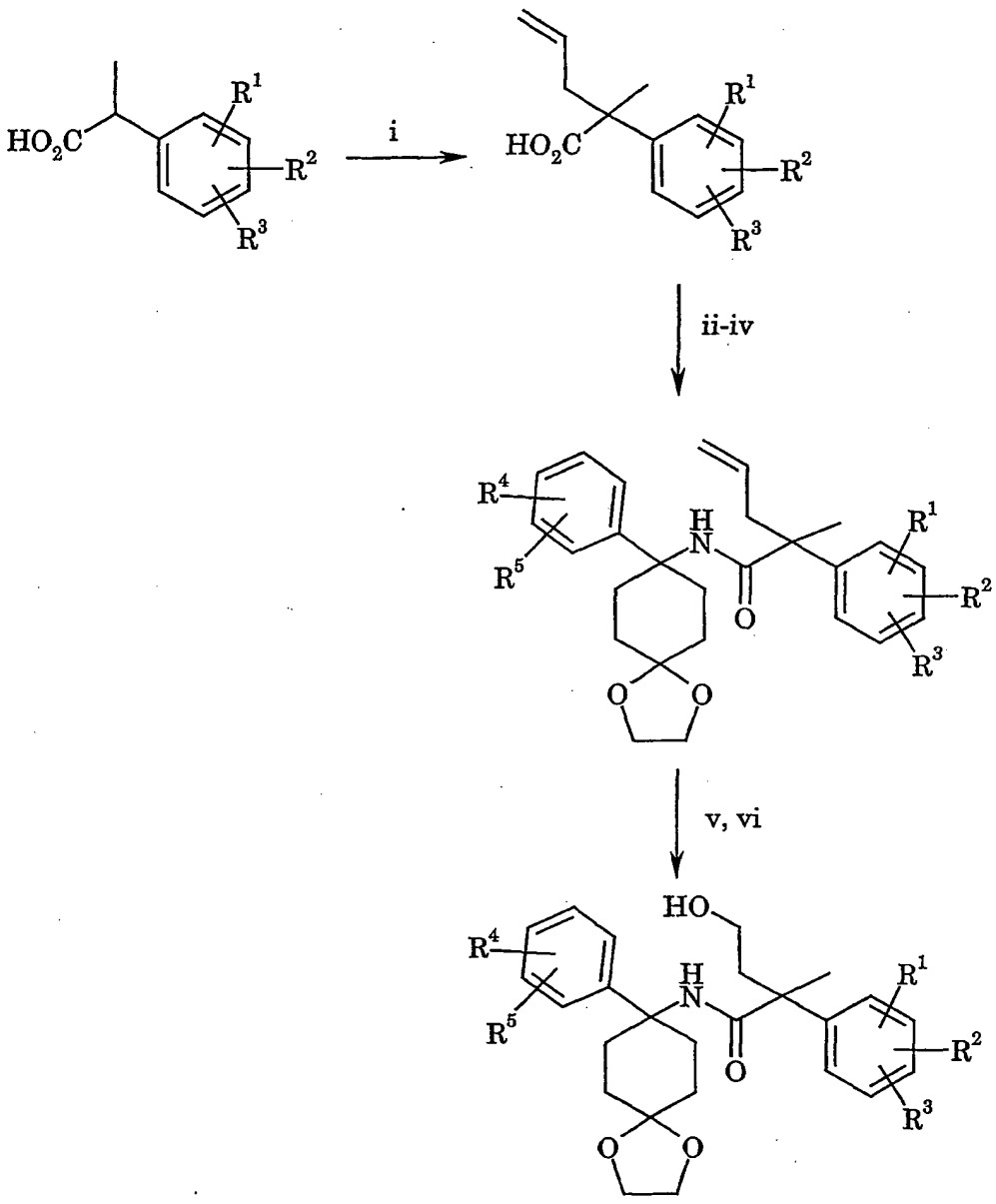


(II)

Appropriate reagents for each of the steps (i) to (x) in Scheme 3 may be as follows:

(i)	nBuLi;	(vi)	4-oxo-1-phenylcyclohexylamine, Py;
(ii)	$BrCH_2CH_2CH=CH_2$;	(vii)	$HOCH_2CH_2OH$, pTsOH, $PhCH_3$;
(iii)	dicyclohexylamine, recrystallise;	(viii)	O_3;
(iv)	citric acid, EtOAc, H_2O;	(ix)	$NaBH_4$; and
(v)	$(COCl)_2$, DMF, CH_2Cl_2;	(x)	CBr_4, Ph_3P, Py.

Scheme 4



(III)

Appropriate reagents for each of the steps (i) to (vi) in Scheme 5 may be as follows:

(i) nBuLi, $BrCH_2CH=CH_2$, THF;

(ii) $(COCl)_2$, DMF, CH_2Cl_2;

(iii) 4-amino-4-phenylcyclohexane, Py, CH_2Cl_2;

(iv) $HOCH_2CH_2OH$, pTsOH, $PhCH_3$;

(v) O_3; and

(vi) $NaBH_4$.

The starting materials in each of the above Schemes 2, 3 and 4 are either known compounds or may be prepared by conventional methods, for instance by methods analogous to those described herein.

It will be appreciated that the general methodology described above may be adapted, using methods that are readily apparent to one of ordinary skill in the art, in order to prepare further compounds of the present invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds were found to be active with IC_{50} at the NK_1 receptor of less than 100nM on said test method.

The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

DESCRIPTION 1

Dimethyl 4-Oxo-1-phenyl-1,3-cyclohexanedicarboxylate

Sodium hydride (60% in mineral oil, 35.8 g, 1.49 mol) was washed with hexane to remove the mineral oil, suspended in dimethylformamide (400 mL) and cooled to 0 °C. Methyl phenyl acetate (42 mL, 0.3 mol) was added slowly with stirring. Methyl acrylate (59 mL, 0.65 mol) was added dropwise over 2 hours at 0 °C and the mixture was stirred at room temperature overnight. Aqueous ammonium chloride (saturated) was added and the mixture was extracted with dichloromethane (2 x 700 mL). The combined organic fractions were washed with water (5 x 500 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue purified by flash column chromatography on silica gel, eluting with isohexane/Et_2O (80:20) and the residue was triturated with isohexane-Et_2O (50:50). The solid was collected and dried *in vacuo* to give the title compound as colourless crystals (30 g, 35%). ^1H NMR (400MHz, $CDCl_3$) δ 12.11 (1H, s), 7.36-7.25 (5H, m), 3.81 (3H, s), 3.64 (3H, s), 3.08 (1H, d, *J* 16.1 Hz), 2.73 (1H, d, *J* 16.1 Hz), 2.26-2.37 (2H, m), and 2.22-2.17 (2H, m).

DESCRIPTION 2

4-Oxo-1-phenylcyclohexanecarboxylic Acid

Lithium hydroxide monohydrate (11.08 g, 264 mmol) was added to a suspension of dimethyl 4-oxo-1-phenyl-1,3-cyclohexanedicarboxylate (Description 1, 25.5 g, 87.9 mmol) in methanol (250 mL), water (83 mL) and tetrahydrofuran (83 mL) and the mixture was heated under reflux for 3 days. The mixture was cooled and the tetrahydrofuran and methanol were evaporated under reduced pressure. The pH was adjusted to 1 with hydrochloric acid (5M) and the mixture was extracted with dichloromethane. The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a light yellow solid (19 g, 99%). ^1H NMR (400MHz, $CDCl_3$) δ 7.50-7.29 (5H, m), 2.29-2.73 (2H, m), 2.62-2.55 (2H, m), 2.47-2.41 (2H, m), and 2.35-2.27 (2H, m).

DESCRIPTION 3

4-Oxo-1-phenylcyclohexylamine Hydrochloride

Diphenylphosphoryl azide (18.8 mL, 23.9 g, 87 mmol) was added to a solution of 4-oxo-1-phenylcyclohexanecarboxylic acid (Description 2, 17.1 g, 78 mmol) and triethylamine (24.4 mL, 17.7 g, 175 mmol) in toluene (260 mL) and the mixture was stirred at 90 °C for 90 minutes. The mixture was cooled, diluted with ethyl acetate (300 mL) and washed with sodium carbonate (2 x 250 mL). The combined aqueous fractions were extracted with ethyl acetate (300 mL) and the combined organic fractions were washed with brine (250 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was suspended in hydrochloric acid (5M, 500 mL) and the mixture was heated under reflux for 2 hours. The mixture was cooled; the solvent was evaporated under reduced pressure and the residue was dried azeotropically by evaporating toluene under reduced pressure (4 x) to give crude title compound which was used without further purification. m/z (ES^+) 190 (M+1)

DESCRIPTION 4

Dicyclohexylammonium (*RS*)-α-Methyl-3,5-bis(trifluoromethyl)benzeneacetate

n-Butyllithium (2.5M solution in hexanes, 67.6 mL, 169 mmol) was added slowly to a stirred, cooled (-78 °C) solution of 3,5-bis(trifluoromethyl)benzeneacetic acid (20.0 g, 73.5 mmol) in tetrahydrofuran (400 mL) and the mixture was stirred at -78 °C for 1 hour. Iodomethane (6.87 mL, 110 mmol) was added slowly and the mixture was allowed to warm to room temperature and stirred overnight. Aqueous sodium bisulfite (20%) was added until the mixture was acidic. The mixture was extracted with ethyl acetate, the combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (400 mL), dicyclohexylamine (10 mL, 80.85 mmol) was added and the mixture was heated under reflux for 1 hour. The mixture was cooled and the solid was collected and dried *in vacuo* to give the title compound as a colourless solid (31.13 g, 91%). ^1H NMR (400MHz, $CDCl_3$) δ 7.83 (2H, s), 7.68 (1H, s), 3.66 (1H, q, *J* 7.1 Hz), 2.83-2.75 (2H, m), 1.87-1.84 (4H, m), 1.71-1.68 (4H, m), 1.60-1.57 (2H, m), 1.48 (3H, d, *J* 7.1 Hz), 1.28-1.08 (8H, m), and 1.03-0.92 (2H, m).

DESCRIPTION 5

Dicyclohexylammonium (*RS*)-α-(3-Butenyl)-3,5-bis(trifluoromethyl)benzeneacetate

Prepared from 3,5-bis(trifluoromethyl)benzeneacetic acid and 4-bromo-1-butene according to the method of Description 4. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (2H, s), 7.69 (1H, s), 5.86-5.75 (1H, s), 5.00-4.95 (2H, m), 3.51 (1H, t, *J* 7.5 Hz), 2.84-2.77 (2H, m), 2.24-2.15 (1H, m), 2.08-1.99 (2H, m), 1.87 (4H, d, *J* 10 Hz), 1.82-1.73 (1H, m), 1.69 (4H, d, *J* 13 Hz), 1.58 (4H, d, *J* 13 Hz), 1.30-1.08 (8H, m), and 1.00-0.93 (2H, m).

DESCRIPTION 6

Dicyclohexylammonium (*RS*)-α-(2-Propenyl)-3,5-bis(trifluoromethyl)benzeneacetate

Prepared from 3,5-bis(trifluoromethyl)benzeneacetic acid and 3-bromo-1-propene according to the method of Description 4. ^{1}H NMR (400MHz, CD_3OD) δ 7.95 (2H, s), 7.75 (1H, s), 5.82-5.70 (1H, m), 5.01 (1H, br d, *J* 17 Hz), 4.93 (1H, br d, *J* 10 Hz), 3.65 (1H, t, *J* 7 Hz), 3.20-3.10 (2H, m), 2.87-2.77 (1H, m), 2.53-2.43 (1H, m), 2.10-2.00 (4H, m), 1.90-1.80 (4H, m), 1.75-1.65 (2H, m), and 1.45-1.12 (10H, m).

DESCRIPTION 7

(*RS*)-α-Methyl-3,5-bis(trifluoromethyl)benzeneacetic Acid

Dicyclohexylammonium (*RS*)-α-methyl-3,5-bis(trifluoromethyl)benzeneacetate (Description 4, 31.13 g, 67 mmol) was suspended in ethyl acetate and washed with aqueous citric acid (25%) and water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colourless solid (19.0 g, 100%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (1H, s), 7.78 (2H, s), 3.90 (1H, q, *J* 7.2 Hz), and 1.60 (3H, d, *J* 7.2 Hz).

DESCRIPTION 8

(*RS*)-α-(3-Butenyl)-3,5-bis(trifluoromethyl)benzeneacetic Acid

Prepared from dicyclohexylammonium (*RS*)-α-(3-butenyl)-3,5-bis(trifluoromethyl)benzeneacetate (Description 5) according to the method of Description 7. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (1H, s), 7.78 (2H, s), 5.80-5.70

(1H, s), 5.05-4.98 (2H, m), 3.78-3.73 (1H, m), 2.32-2.23 (1H, m), 2.11-2.00 (2H, m), and 1.96-1.85 (1H, m).

DESCRIPTION 9

(*RS*)-α-(2-Propenyl)-3,5-bis(trifluoromethyl)benzeneacetic Acid

Prepared from dicyclohexylammonium (*RS*)-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetate (Description 6) according to the method of Description 7. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (1H, s), 7.78 (2H, s), 5.68 (1H, m), 5.15-5.05 (2H, m), 3.82 (1H, t, *J* 7.6 Hz), 2.90 (1H, ddd, *J* 14, 7, 7 Hz), and 2.58 (1H, ddd, *J* 14, 7, 7 Hz).

DESCRIPTION 10

(*RS*)-α-Methyl-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetic Acid

n-Butyllithium (2.5M solution in hexanes, 61.0 mL, 153 mmol) was added slowly to a stirred, cooled (-78 °C) solution of (*RS*)-α-methyl-3,5-bis(trifluoromethyl)benzeneacetic acid (Description 7, 19.0 g, 66.4 mmol) in tetrahydrofuran (400 mL) and the mixture was stirred at -78 °C for 2 hours. Further n-butyllithium (2.5M solution in hexanes, 8.0 mL, 20 mmol) was added slowly and the mixture was stirred at -78 °C for 20 minutes. Further n-butyllithium (2.5M solution in hexanes, 8.0 mL, 20 mmol) was added slowly and the mixture was stirred at -78 °C for 20 minutes. 3-Bromo-1-propene (8.62 mL, 12.05 g, 100 mmol) was added slowly and the mixture was stirred at -78 °C for 30 minutes, then at room temperature for 1 hour. The mixture was poured into aqueous sodium bisulfite (10%, 500 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic fractions were washed with brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was triturated with hexane and the solid was collected and dried *in vacuo* to give the title compound as a colourless solid (10.59 g, 49%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.82 (2H, s), 7.81 (1H, s), 5.57 (1H, m), 5.13 (1H, s), 5.10 (1H, m), 2.86 (1H, m), 2.73 (1H, m), and 1.69 (3H, s).

DESCRIPTION 11

(*RS*)-α-(3-Butenyl)-N-(4-oxo-1-phenylcyclohexyl)-3,5-bis(trifluoromethyl)-benzeneacetamide

Oxalyl chloride (4.22 mL, 48.4 mmol) was added to a solution of (*RS*)-α-(3-butenyl)-3,5-bis(trifluoromethyl)benzeneacetic acid (Description 8, 24.2 mmol) and dimethylformamide (0.1 mL) in dichloromethane (80 mL) and the mixture was stirred at room temperature for 3 hours. The solvent was evaporated under reduced pressure and toluene was added and evaporated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and added to a stirred, cooled (0 °C) solution of 4-oxo-1-phenylcyclohexylamine hydrochloride (Description 3, 4.58 g, 24.2 mmol) in dichloromethane (150 mL). Pyridine (4.1 mL, 50.8 mmol) was added and the mixture was stirred at room temperature overnight. The mixture was washed with hydrochloric acid (1M, 2 x 200 mL), saturated aqueous sodium hydrogen carbonate (2 x 200 mL) and brine (200 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was triturated with isohexane/diethylether (7:1) and the solid was collected and dried *in vacuo*. The solid was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (2:1), to give the title compound (6.22g, 52%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 (1H, s), 7.73 (2H, s), 7.31-7.25 (5H, m), 5.80-5.70 (2H, m), 5.05-4.97 (2H, m), 3.52-3.47 (1H, m), 2.86-2.80 (1H, m), 2.65-2.57 (1H, m), 2.50-2.31 (6H, m), 2.27-2.18 (1H, m), 2.09-1.95 (2H, m), and 1.81-1.72 (1H, m).

DESCRIPTION 12

(*RS*)-N-(4-Oxo-1-phenylcyclohexyl)-α-(2-propenyl)-3,5-bis(trifluoromethyl)-benzeneacetamide

Prepared from (*RS*)-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetic acid (Description 9) and 4-oxo-1-phenylcyclohexylamine hydrochloride (Description 3) according to the method of Description 11. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 (1H, s), 7.73 (2H, s), 7.35-7.2 (5H, m), 5.80 (1H, br s), 5.75-5.63 (1H, m), 5.13-5.05 (2H, m), 3.56 (1H, dd, *J* 7, 6 Hz), 2.90-2.80 (2H, m), 2.65-2.55 (1H, m), and 2.52-2.30 (7H, m).

DESCRIPTION 13

(*RS*)-N-(4-Oxo-1-phenylcyclohexyl)-α-methyl-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetamide

Prepared from (*RS*)-α-methyl-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetic acid (Description 10) and 4-oxo-1-phenylcyclohexylamine hydrochloride (Description 3) according to the method of Description 11. ^{1}H NMR (360MHz, $CDCl_3$) δ 7.81 (1H, s), 7.71 (2H, s), 7.35-7.27 (5H, m), 5.58 (1H, br s), 5.57-5.45 (1H, m), 5.09-5.03 (2H, m), 2.81-2.73 (2H, m), 2.66-2.60 (2H, m), 2.48-2.30 (6H, m), and 1.63 (3H, s).

DESCRIPTION 14

(*RS*)-α-(3-Butenyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide

Ethylene glycol (1.39 mL, 25 mmol) and *p*-toluenesulfonic acid (71 mg, 0.37 mmol) were added to a solution of (*RS*)-α-(3-butenyl)-N-(4-oxo-1-phenylcyclohexyl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 11, 6.22 g, 12.5 mmol) in toluene (200 mL) and the mixture was heated under reflux with azeotropic removal of water overnight. The mixture was cooled, potassium carbonate (13 g) was added and the mixture was stirred at room temperature for 10 minutes. Water (100 mL), aqueous sodium carbonate (10%, 100 mL) and ethyl acetate (200 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 200 mL) and the combined organic fractions were washed with brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude title compound (9.1 g) which was used without further purification. ^{1}H NMR (400MHz, $CDCl_3$) contains residual toluene δ 7.79 (1H, s), 7.73 (2H, s), 7.27-7.14 (5H, m), 5.79-5.72 (2H, m), 5.63 (1H, s), 5.05-4.99 (2H, m), 3.97-3.92 (4H, m), 3.49-3.45 (1H, m), 2.56-2.52 (1H, m), 2.25-2.12 (4H, m), 2.05-1.99 (2H, m), and 1.77-1.59 (5H, m).

DESCRIPTION 15

(*RS*)-N-(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetamide

Prepared from (*RS*)-N-(4-oxo-1-phenylcyclohexyl)-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 12) according to the method of Description 14. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.79 (1H, s), 7.73 (2H, s), 7.30-7.15 (5H, m), 5.75-5.60 (2H, m), 5.08 (1H, d, *J* 8 Hz), 5.04 (1H, s), 4.0-3.8 (4H, m), 3.52 (1H, t, *J* 7 Hz), 2.88-2.78 (1H, m), 2.58-2.48 (1H, m), 2.47-2.37 (1H, m), 2.26-2.06 (3H, m), and 1.75-1.55 (4H, m).

DESCRIPTION 16

(*RS*)-N-(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)-α-methyl-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetamide

Prepared from (*RS*)-N-(4-oxo-1-phenylcyclohexyl)-α-methyl-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 13) according to the method of Description 14. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (1H, s), 7.73 (2H, s), 7.30-7.19 (5H, m), 5.53-5.43 (2H, m), 5.08-5.02 (2H, m), 3.98-3.90 (4H, m), 2.80-2.74 (1H, m), 2.63-2.57 (1H, m), 2.48-2.43 (1H, m), 2.26-2.06 (3H, m), and 1.71-1.52 (7H, m).

DESCRIPTION 17

(*RS*)-α-(3-Hydroxypropyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide

Crude (*RS*)-α-(3-butenyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 14, 9.1 g) was dissolved in methanol/dichloromethane (1:1, 120 mL) and cooled to –78 °C. Oxygen was bubbled through the solution for 10 minutes, then ozone was bubbled through until the solution had gone from orange to grey/brown (about 50 minutes). The reaction was flushed with oxygen for 10 minutes, then with nitrogen for 10 minutes. Sodium borohydride (4.7 g, 125 mmol) was added and the mixture was stirred at -78 °C for 1 hour, then at room temperature overnight. Further portions of sodium borohydride (470 mg, 12.5 mmol) were added at 30 minutes intervals until effervescence ceased. Acetone

(60 mL) was added and the mixture was stirred at room temperature for 10 minutes. Water (60 mL) was added and the solvent was evaporated under reduced pressure. Aqueous citric acid (10%, 150 mL) and ethyl acetate (150 mL) were added and the mixture was stirred for 30 minutes. The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic fractions were washed with water (2 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/isohexane (75:25), to give the title compound (5.38 g, 79 % from (*RS*)-α-(3-butenyl)-N-(4-oxo-1-phenylcyclohexyl)-3,5-bis(trifluoromethyl)benzeneacetamide). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.79 (1H, s), 7.74 (2H, s), 7.23-7.17 (5H, m), 5.83 (1H, s), 3.97-3.93 (4H, m), 3.70-3.56 (3H, m), 2.57-2.53 (1H, m), 2.26-2.08 (4H, m), and 1.77-1.52 (8H, m).

DESCRIPTION 18

(*RS*)-α-(2-Hydroxyethyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide

Prepared from (*RS*)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 15) according to the method of Description 17. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 (1H, s), 7.78 (2H, s), 7.30-7.15 (5H, m), 5.93 (1H, br s), 4.0-3.9 (4H, m), 3.86 (1H, dd, *J* 9, 5.7 Hz), 3.70-3.50 (2H, m), 2.60-2.50 (1H, m), 2.39-2.28 (1H, m), 2.27-2.08 (3H, m), 2.00-1.83 (2H, m), and 1.78-1.60 (4H, m).

DESCRIPTION 19

(*RS*)-α-(2-Hydroxyethyl)-α-methyl-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide

Prepared from (*RS*)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-α-methyl-α-(2-propenyl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 16) according to the method of Description 17. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.82 (1H, s), 7.75 (2H, s), 7.31-7.20 (5H, m), 5.77 (1H, br s), 3.98-3.91 (4H, m), 3.69-3.62 (1H, m), 3.60-3.54

(1H, m), 2.50-2.45 (1H, m), 2.37-2.30 (1H, m), 2.24-2.17 (2H, m), 2.14-2.06 (2H, m), 1.99-1.89 (1H, m), and 1.75-1.53 (7H, m).

DESCRIPTION 20

(*RS*)-α-(3-Bromopropyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide

Triphenylphosphine (3.85 g, 14.66 mmol) in dichloromethane (50 mL) was added slowly to a stirred, cooled (0 °C) suspension of (*RS*)-α-(3-hydroxypropyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 17, 3.2 g, 5.87 mmol) and carbon tetrabromide (4.86 g, 14.7 mmol) in dichloromethane (50 mL) and the mixture was stirred at 0 °C for 15 minutes then at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (80:20), to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.81 (1H, s), 7.73 (2H, s), 7.25-7.17 (5H, m), 5.65 (1H, s), 3.98-3.91 (4H, m), 3.49-3.31 (3H, m), 2.51-2.48 (1H, m), 2.26-2.09 (4H, m), and 1.91-1.56 (7H, m).

DESCRIPTION 21

(*RS*)-α-(2-Bromoethyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide

Prepared from (*RS*)-α-(2-hydroxyethyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 18) according to the method of Description 20. m/z (ES^+) 594, 596 (M+1).

DESCRIPTION 22

1-(1,1-Dimethylethyl) 4-Ethyl 4-(2-Propenyl)-1,4-piperidinedicarboxylate

A solution of 1-(1,1-dimethylethyl) 4-ethyl 1,4-piperidinedicarboxylate (25.0 g, 97 mmol) in tetrahydrofuran (100 mL) was added slowly to a stirred, cooled (-78 °C) solution of potassium hexamethyldisilazide (29.0 g, 145 mmol) in tetrahydrofuran (150 mL), maintaining the internal temperature below -65 °C. The mixture was stirred at -78 °C for 30 minutes, then 3-bromopropene (12.6 mL, 145 mmol) was added dropwise over 10 minutes. The mixture was stirred at -78 °C for 1 hour, then

saturated aqueous ammonium chloride (400 mL) and water (100 mL) were added and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate (3 x 400 mL) and the combined organic fractions were washed with aqueous citric acid (10%, 2 x 250 mL), saturated aqueous sodium hydrogen carbonate (400 mL) and brine (200 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound (29.3 g, 100%). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.75-5.60 (1H, m), 5.10-5.00 (2H, m), 4.16 (2H, q, *J* 7 Hz), 3.92-3.78 (2H, m), 2.90 (2H, br t, *J* 14 Hz), 2.26 (2H, d, *J* 7 Hz), 2.08 (2H, br d, *J* 14 Hz), 1.45 (9H, s), 1.45-1.30 (2H, m), and 1.26 (3H, t, *J* 7 Hz).

DESCRIPTION 23

1,1-Dimethylethyl 1-Oxo-2-oxa-8-azaspiro[4.5]decane-8-carboxylate

1-(1,1-Dimethylethyl) 4-ethyl 4-(2-propenyl)-1,4-piperidinedicarboxylate (Description 22, 20.0 g, 67.2 mmol) was dissolved in methanol (300 mL) and dichloromethane (300 mL) and cooled to -78 °C. Oxygen was bubbled through the solution for 10 minutes, then ozone for 75 minutes, to give a persistent blue coloration. Oxygen was bubbled through the solution for 10 minutes, then nitrogen for 10 minutes. Sodium borohydride (5.1 g, 135 mmol) was added and the mixture was stirred at -78 °C for 1 hour. Further sodium borohydride (5.1 g, 135 mmol) was added and the mixture was stirred at room temperature for 16 hours. Acetone (75 mL) was added and the mixture was stirred at room temperature for 10 minutes. Water (50 mL) was added and the organic solvent was evaporated under reduced pressure. Saturated aqueous ammonium chloride (500 mL) was added and the mixture was extracted with ethyl acetate (2 x 500 mL). The combined organic fractions were washed with aqueous citric acid (10%, 500 mL), saturated aqueous sodium hydrogen carbonate (500 mL) and brine (200 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound (15.0 g, 88%). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.31 (2H, t, *J* 7 Hz), 3.97-3.87 (2H, m), 3.17-3.07 (2H, m), 2.20 (2H, t, *J* 7 Hz), 1.92-1.82 (2H, m), 1.60-1.45 (2H, m), and 1.45 (9H, s).

DESCRIPTION 24

1,1-Dimethylethyl 4-(2-Hydroxyethyl)-4-(hydroxymethyl)-1-piperidinecarboxylate

Diisobutylaluminium hydride (1.0M in dichloromethane, 3.60 mL, 3.60 mmol) was added over 10 minutes to a stirred, cooled (-78 °C) solution of 1,1-dimethylethyl 1-oxo-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (Description 23, 400 mg, 1.57 mmol) in dichloromethane (4 mL) and the mixture stirred at -78 °C for 3 hours, then at 0 °C for 2 hours. Water (1.6 mL) was added very slowly at 0 °C and the mixture was warmed to room temperature and stirred overnight. The mixture was filtered through Hyflo™, washing with dichloromethane, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate, to give the title compound (255 mg, 63%). m/z (ES^+) 260 (M+1).

DESCRIPTION 25

1,1-Dimethylethyl 2-Oxa-8-azaspiro[4.5]decane-8-carboxylate

Diethyl azodicarboxylate (183 µl, 1.16 mmol) in tetrahydrofuran (0.5 mL) was added dropwise to a stirred, cooled (0 °C) solution of 1,1-dimethylethyl 4-(2-hydroxyethyl)-4-(hydroxymethyl)-1-piperidinecarboxylate (Description 24, 250 mg, 0.96 mmol) and triphenylphosphine (303 mg, 1.16 mmol) in tetrahydrofuran (10 mL) and the mixture was stirred at 0 °C for 90 minutes then at room temperature overnight. The mixture was cooled to 0 °C and further triphenylphosphine (126 mg, 0.48 mmol) and diethyl azodicarboxylate (76 µl, 0.48 mmol) were added. The mixture was stirred at room temperature for 2.5 hours, then the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (80:20), to give the title compound as a colorless oil (150 mg, 65%). m/z (ES^+) 186 (M+1-C_4H_8).

DESCRIPTION 26

2-Oxa-8-azaspiro[4.5]decane

Methanolic hydrogen chloride (3M, 3 mL) was added to a stirred, cooled (0 °C) solution of 1,1-dimethylethyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate (Description 25, 150 mg, 0.62 mmol) in methanol and the mixture was stirred at room temperature

for 24 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in methanol and passed through Amberlyst™ 26 ion exchange resin, eluting with methanol. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound (77 mg, 88%). m/z (ES^+) 142 (M+1).

EXAMPLE 1

(*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-piperidinone

Sodium hexamethyldisilazide (1.0M in tetrahydrofuran, 1.64 mL, 1.64 mmol) was added dropwise under argon to a stirred, cooled (-78 °C), rigourously degassed solution of (*RS*)-α-(3-bromopropyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 20, 1.0 g, 1.64 mmol) in tetrahydrofuran (20 mL) and the mixture was stirred at -78 °C for 5 minutes, then at room temperature for 30 minutes. The mixture was cooled to -78 °C and further sodium hexamethyldisilazide (1.0M in tetrahydrofuran, 0.5 mL, 0.5 mmol) was added. The mixture was stirred at room temperature for 30 minutes, then saturated aqueous ammonium chloride (10 mL) and water (20 mL) were added. The mixture was extracted with ethyl acetate (2 x 20 mL), and the combined organic fractions were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (67:33). The residue was purified by MPLC on silica gel, eluting with isohexane/EtOAc (67:33), to give the title compound (510 mg, 59%). ^1H NMR (400MHz, $CDCl_3$) δ 7.73 (1H, s), 7.62 (2H, s), 7.50 (2H, dd, *J* 1.0, 8.4 Hz), 7.35-7.31 (2H, m), 7.27-7.22 (1H, m), 4.00-3.93 (4H, m), 3.79 (1H, dd, *J* 6.8, 10.0 Hz), 3.45 (1H, d, *J* 4.7 Hz), 3.45-3.42 (1H, m), 2.91-2.88 (1H, m), 2.79-2.75 (1H, m), 2.34-2.16 (3H, m), and 1.95-1.63 (7H, m).

EXAMPLE 2

(*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone

Sodium hydride (60% dispersion in mineral oil, 40 mg, 1.00 mmol) was added to a rigourously degassed solution of (*RS*)-α-(2-bromoethyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 21, 600 mg, 1.01 mmol) in tetrahydrofuran (15 mL) and the mixture was stirred at room temperature for 1 hour. Further sodium hydride (60% dispersion in mineral oil, 40 mg, 1.00 mmol) was added and the mixture was stirred at room temperature for 20 minutes. Saturated ammonium chloride (5 mL) and water (10 mL) were added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was triturated with isohexane (2 x 5 mL) and the solid was collected and dried *in vacuo* to give the title compound (455 mg, 88%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.78 (1H, s), 7.70 (2H, s), 7.47 (2H, d, *J* 7 Hz), 7.34 (2H, t, *J* 7 Hz), 7.30-7.25 (1H, m), 4.02-3.92 (4H, m), 3.80 (1H, t, *J* 9.5 Hz), 3.39 (2H, m), 2.93 (1H, br d, *J* 13 Hz), 2.80 (1H, br d, *J* 13 Hz), 2.52-2.42 (1H, m), 2.33-2.23 (1H, m), 2.22-2.12 (1H, m), 2.12-2.01 (1H, m), and 1.90-1.70 (4H, m). m/z (ES^+) 514 (M+1).

EXAMPLE 3

(*RS*)-3-Hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone

Sodium hydride (60% dispersion in mineral oil, 150 mg, 3.75 mmol) was added to a solution of (*RS*)-α-(2-bromoethyl)-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 21, 430 mg, 0.723 mmol) in tetrahydrofuran (5 mL) and the mixture was stirred at room temperature for 20 hours. Aqueous citric acid (10%, 20 mL) was added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were washed with water (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (75:25 increasing to 50:50), to give the title compound (142 mg,

38%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (3H, s), 7.48 (2H, d, *J* 7 Hz), 7.37 (2H, t, *J* 7 Hz), 7.30 (1H, t, *J* 7 Hz), 4.02-3.90 (4H, m), 3.40 (1H, dt, *J* 8, 3 Hz), 3.23 (1H, q, *J* 8 Hz), 2.98 (1H, br d, *J* 13 Hz), 2.72 (1H, br d, *J* 13 Hz), 2.48-2.18 (4H, m), 1.85-1.65 (4H, m), and 1.6 (1H, br s).

EXAMPLE 4

(*RS*)-3-Methyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone

Sodium hexamethyldisilazide (1M in tetrahydrofuran, 8.8 mL, 8.8 mmol) was added dropwise to a stirred, cooled (-78 °C) solution of (*RS*)-α-(2-hydroxyethyl)-α-methyl-N-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-3,5-bis(trifluoromethyl)benzeneacetamide (Description 19, 2.09 g, 3.83 mmol) in tetrahydrofuran (100 mL) and the mixture was stirred at -78 °C for 30 minutes. Methanesulfonyl chloride (0.44 mL, 0.66 g, 5.8 mmol) was added and the mixture was stirred at -78 °C for 10 minutes, then allowed to warm to room temperature. Saturated aqueous ammonium chloride (100 mL) and water (20 mL) were added and the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (75:25 increasing to 70:30), to give the title compound (340 mg, 17%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (2H, s), 7.75 (1H, s), 7.45-7.23 (5H, m), 3.95 (4H, m), 3.28 (1H, m), 3.20 (1H, m), 2.86 (2H, m), 2.36 (1H, m), 2.23 (2H, m), 2.11 (1H, m), 1.72 (4H, m), and 1.51 (3H, s).

EXAMPLE 5

(*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-piperidinone

Hydrochloric acid (2M, 15 mL) was added to a solution of (*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-piperidinone (Example 1, 210 mg, 0.59 mmol) in acetone (15 mL) and the mixture was heated at 50 °C for 5 hours. The mixture was cooled, neutralised with aqueous sodium carbonate (10%) and extracted with ethyl acetate (75 mL). The organic fraction was washed with brine, dried ($MgSO_4$) and the solvent was evaporated under

reduced pressure to give the title compound (275 mg, 96%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.76 (1H, s), 7.63 (2H, s), 7.52-7.49 (2H, m), 7.41-7.37 (2H, m), 7.33-7.29 (1H, m), 3.83 (1H, dd, *J* 6.8, 10.0 Hz), 3.43 (2H, t, *J* 5.9 Hz), 3.18-3.13 (1H, m), 3.09-3.04 (1H, m), 2.63-2.55 (1H, m), 2.52-2.33 (5H, m), 2.25-2.21 (1H, m), and 1.97-1.81 (3H, m).

EXAMPLE 6

(*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-pyrrolidinone

Prepared from (*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone (Example 2) according to the method of Example 5. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.80 (1H, s), 7.71 (2H, s), 7.52-7.28 (5H, m), 3.85 (1H, t, *J* 9.5 Hz), 3.42-3.38 (2H, m), 3.23-3.07 (2H, m), 2.70-2.30 (7H, m), and 2.18-2.05 (1H, m). m/z (ES^+) 470 (M+1).

EXAMPLE 7

(*RS*)-3-Hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-pyrrolidinone

Prepared from (*RS*)-3-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone (Example 3) according to the method of Example 5. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.82 (1H, s), 7.80 (2H, s), 7.53-7.33 (5H, m), 3.45-3.38 (1H, m), 3.29-3.19 (2H, m), 3.10-3.00 (1H, m), and 2.60-2.30 (8H, m).

EXAMPLE 8

(*RS*)-3-Methyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone

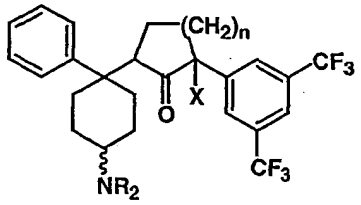
Prepared from (*RS*)-3-methyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)-2-pyrrolidinone (Example 4) according to the method of Example 5. ^{1}H NMR (360MHz, $CDCl_3$) δ 7.86 (2H, s), 7.77 (1H, s), 7.46-7.29 (5H, m), 3.22 (3H, m), 3.07 (1H, m), 2.58-2.28 (7H, m), 2.15 (1H, m), and 1.54 (3H, s).

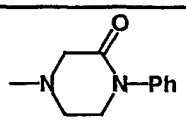
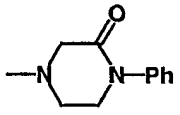
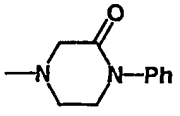
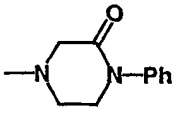
EXAMPLE 9

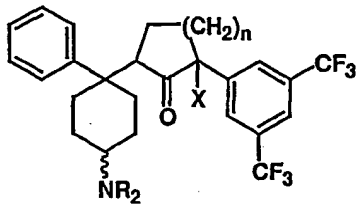
Cis-(*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone and *Trans*-(*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone

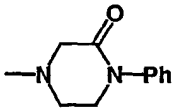
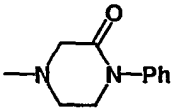
Triethylamine (56 µl, 0.40 mmol) was added to a suspension of 2-oxa-8-azaspiro[4.5]decane hydrochloride (Description 26, 55 mg, 0.31 mmol) in 1,2-dichloroethane (10 mL) and the mixture was sonicated until the solid dissolved. (*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-piperidinone (Example 5, 100 mg, 0.21 mmol) and sodium triacetoxyborohydride (49 mg, 0.23 mmol) were added and the mixture was stirred at room temperature overnight. Further portions of sodium triacetoxyborohydride (22 mg, 0.1 mmol) were added at 4 hour intervals until the reaction was complete (monitoring by HPLC). The mixture was poured into saturated aqueous sodium hydrogen carbonate (30 mL) and extracted with dichloromethane (30 mL). The organic fraction was washed with brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (1.5 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 2 mL), then eluted with methanolic ammonia (2M, 2 x 2 mL). The solvent was evaporated under reduced pressure and the residue was purified by MPLC on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (96:4:0.4) to give cis-*(RS)-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone*; ^{1}H NMR (400MHz, CD_3OD) δ 7.86 (3H, s), 7.47 (2H, d, *J* 7.4 Hz), 7.36 (2H, t, *J* 7.4 Hz), 7.25 (1H, t, *J* 7.4 Hz), 4.05 (1H, dd, *J* 10.7, 6.9 Hz), 3.90 (2H, t, *J* 7.1 Hz), 3.60-3.05 (11H, m), 2.23 (1H, m), 2.13-2.00 (3H, m), and 1.90-1.64 (12H, m); m/z (ES^+) 608 (M+1); and trans-*(RS)-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone*; ^{1}H NMR (400MHz, CD_3OD) δ 7.76 (1H, s), 7.63 (2H, d, *J* 7.5 Hz), 7.57 (2H, s), 7.37 (2H, t, *J* 7.5 Hz), 7.26 (1H, t, *J* 7.5 Hz), 3.86 (2H, m), 3.76 (1H, dd, *J* 9.6, 6.7 Hz), 3.66 (2H, t, *J* 5.5 Hz), 3.51-3.30 (6H, m), 3.15 (1H, m), 3.02 (2H, br m), 2.37-2.08 (5H, m), 1.94-1.79 (9H, m), 1.63 (1H, m), and 1.45 (1H, m); m/z (ES^+) 608 (M+1).

The following compounds were prepared from (*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-piperidinone (Example 5), (*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-pyrrolidinone (Example 6), (*RS*)-3-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-pyrrolidinone (Example 7) or (*RS*)-3-methyl-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-pyrrolidinone (Example 8), according to the method of Example 9, substituting a suitable amine for 2-oxa-8-azaspiro[4.5]decane.



Ex.	n	X	-NR_2	Stereochemistry	Formula	M.W.	m/z (ES^+) (M+1)
10[1]	2	H		*Cis*-(*RS*)-	$C_{35}H_{35}F_6N_3O_2$	643	644
11[1]	2	H		*Trans*-(*RS*)-	$C_{35}H_{36}N_3O_2F_6$	643	644
12	1	H		*Cis*-(*RS*)-	$C_{32}H_{36}F_6N_2O_2$	594	595
13	1	H		*Trans*-(*RS*)-	$C_{32}H_{36}F_6N_2O_2$	594	595
14[1]	1	H		*Cis*-(*RS*)-	$C_{34}H_{33}F_6N_3O_2$	629	630
15[1]	1	H		*Trans*-(*RS*)-	$C_{34}H_{33}F_6N_3O_2$	629	630



Ex.	n	X	-NR$_2$	Stereochemistry	Formula	M.W.	m/z (ES$^+$) (M+1)
16	1	OH		*Cis*-(*RS*)-	$C_{32}H_{36}F_6N_2O_3$	610	611
17	1	OH		*Trans*-(*RS*)-	$C_{32}H_{36}F_6N_2O_3$	610	611
18	1	Me		*Cis*-(*RS*)-	$C_{33}H_{38}F_6N_2O_2$	608	609
19	1	Me		*Trans*-(*RS*)-	$C_{33}H_{38}F_6N_2O_2$	608	609
20[1]	1	Me		*Trans*-(*RS*)-	$C_{35}H_{36}N_3O_2F_6$	643	644
21[1]	1	Me		*Cis*-(*RS*)-	$C_{35}H_{36}N_3O_2F_6$	643	644

[1]1-Phenyl-piperazinone: *Tetrahedron Lett.* **1998**, *39*, 7459-7462.

EXAMPLE 22

Trans-(*RS*)-3-[3,5-Bis(trifluoromethyl)phenyl]-1-(4-dimethylamino-1-phenylcyclohexyl)-2-pyrrolidinone

A solution of zinc chloride (87 mg, 0.064 mmol) and sodium cyanoborohydride (80 mg, 0.13 mmol) in methanol (2 mL) was added to a solution of (*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]-1-(4-oxo-1-phenylcyclohexyl)-2-pyrrolidinone (Example 6, 50 mg, 0.11 mmol) and methanolic dimethylamine (2M, 0.16 mL, 0.32 mmol) in methanol (5 mL) and the mixture was stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure and water (10 mL) was added. The mixture was extracted with ethyl acetate (2 x 10 mL) and the combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with

CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5), then by preparative HPLC (Hichrom RPB 250x21.0 mm i.d.; 0.1% TFA-H_2O/43%MeCN; 20 mL/min; 210 nm; 100 µl injections of a 29 mg/mL solution in MeOH) to give the title compound (2.3 mg, 4%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.75 (1H, s), 7.62 (2H, s), 7.54 (2H, d, *J* 7 Hz), 7.38 (2H, t, *J* 7 Hz), 7.29 (1H, t, *J* 7 Hz), 3.67 (1H, t, *J* 9.2 Hz), 3.40-3.27 (2H, m), 2.93 (1H, br d, *J* 13 Hz), 2.84 (1H, br d, *J* 13 Hz), 2.43-2.23 (4H, m), 2.21 (6H, s), 2.03-1.92 (1H, m), 1.89-1.79 (2H, m), and 1.50-1.33 (2H, m). m/z (ES^+) 500 (M+1).

EXAMPLE 23

Trans-(*RS*)-3-Hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone,
Trans-(*RS*)-3-Methoxy-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone, and
Trans-(*RS*)-3-Methyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone

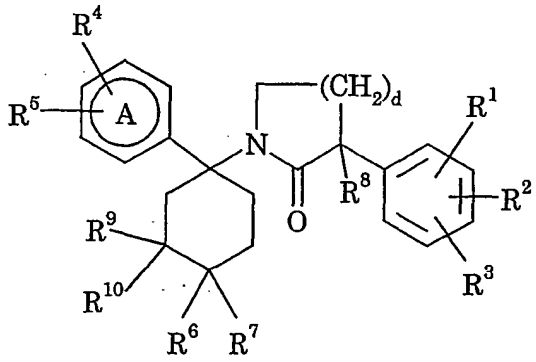
Sodium hydride (60% dispersion in mineral oil; 3 mg, 0.077 mmol) was added to a solution of *trans*-(*RS*)-3-[3,5-bis(trifluoromethyl)phenyl]- 1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone (Example 13, 46 mg, 0.077 mmol) in dimethylformamide (2 mL) and the mixture was stirred at room temperature for 10 minutes. Methyl iodide (4.8 µl, 0.077 mmol) was added and the mixture was stirred at room temperature for 15 minutes. Water (25 mL) was added and the mixture was extracted with ethyl acetate (2 x 25 mL). The combined organic fractions were washed with water (2 x 25 mL) and brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5) to give trans-(RS)-*3-[3,5-bis(trifluoromethyl)phenyl]-3-hydroxy-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone* (10 mg, 21%); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.77 (1H, s), 7.70 (2H, s), 7.54 (2H, dd, *J* 1.3, 8.7 Hz), 7.40 (2H, t, *J* 7.5 Hz), 7.32 (1H, t, *J* 7.25 Hz), 3.81 (2H, t, *J* 7 Hz), 3.49 (2H, s), 3.37-3.31 (1H, m), 3.13-3.03 (2H, m), 2.92 (1H, d, *J* 13 Hz), 2.58-2.45 (5H, m), 2.41-2.26 (3H, m), 2.22-2.16 (1H, m), 1.94-1.88 (2H, m), 1.68 (2H, t, *J* 7 Hz), 1.65-1.58 (4H, m), and 1.47 (2H, q, *J* 10.5 Hz); m/z (ES^+) 611 (M+1).

Mixed fractions were collected and purified by preparative HPLC (ABZ+plus 250x21.0 mm i.d.; 0.1% TFA-H_2O/45%MeCN; 20 mL/min; 210 nm; 75 µl injections of a 45 mg/mL solution in MeOH) to give trans-(RS)-*3-[3,5-bis(trifluoromethyl)phenyl]-3-methoxy-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone* (13 mg, 26%); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.79 (1H, s), 7.77 (2H, s), 7.56-7.53 (2H, m), 7.38-7.34 (2H, m), 7.29-7.26 (1H, m), 3.81 (2H, t, *J* 7 Hz), 3.49 (2H, s), 3.44-3.40 (1H, m), 3.16-3.13 (1H, m), 3.12 (3H, s), 3.03-2.89 (2H, m), 2.42-2.27 (8H, m), 2.08-2.02 (1H, m), 1.86-1.83 (2H, m), 1.69-1.65 (2H, m), 1.57-1.55 (4H, m), and 1.48-1.35 (2H, m); m/z (ES^+) 625 (M+1); and

trans-(RS)-*3-[3,5-bis(trifluoromethyl)phenyl]-3-methyl-1-[4-(2-oxa-8-azaspiro[4.5]decan-8-yl)-1-phenylcyclohexyl]-2-piperidinone* (7 mg, 14%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.73 (2H, s), 7.72 (1H, s), 7.52-7.50 (2H, m), 7.36-7.32 (2H, m), 7.28-7.24 (1H, m), 3.80 (2H, t, *J* 7 Hz), 3.48 (2H, s), 3.25-3.20 (1H, m), 3.15-3.09 (1H, m), 2.97-2.92 (2H, m), 2.47-2.21 (8H, m), 2.06-1.99 (1H, m), 1.86-1.78 (2H, m), 1.68-1.52 (6H, m), 1.56-1.36 (2H, m), and 1.40 (3H, s); m/z (ES^+) 609 (M+1).

CLAIMS:

1. A compound of the formula (I):



(I)

wherein

ring A is a phenyl or pyridyl ring;

R^1 represents hydroxy, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-4}alkyl, C_{1-6}alkoxyC_{1-4}alkoxy, fluoroC_{1-6}alkoxyC_{1-4}alkyl, C_{2-6}alkenyloxy, C_{3-7}cycloalkoxy, C_{3-7}cycloalkylC_{1-4}alkoxy, phenoxy, cyano, halogen, NR^aR^b, SR^a, SOR^a, SO_2R^a, OSO_2R^a, NR^aCOR^c, COR^a, CO_2R^a or $CONR^aR^b$ where R^a and R^b each independently represent hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, fluoroC_{1-4}alkyl or $CH_2CO_2C_{1-4}$alkyl, and R^c represents C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl or phenyl;

R^2 represents hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

or when R^2 is adjacent to R^1, they may be joined together such that there is formed a 5- or 6-membered saturated or unsaturated ring containing one or two atoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by a group selected from C_{1-4}alkyl, CF_3, =O or =S;

R^3 represents hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, cyano, SR^a, SOR^a, SO_2R^a, NR^aR^b, NR^aCOR^c, COR^a, CO_2R^a, $CONR^aR^b$ or C_{1-4}alkyl substituted by cyano, CO_2R^a or $CONR^aR^b$ where R^a, R^b and R^c are as previously defined;

or R^3 represents a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms, selected from nitrogen, oxygen and sulphur, which group is optionally substituted by one or two groups selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, trifluoromethyl, OCF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, phenyl, $-(CH_2)_rNR^aR^b$, $-(CH_2)_rNR^aCOR^b$, $-(CH_2)_rCONR^aR^b$, or $CH_2C(O)R^a$, where R^a and R^b are as previously defined and r is zero, 1 or 2;

R^4 represents hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, hydroxy, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b are as previously defined;

R^5 represents hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl or C_{1-6}alkoxy substituted by C_{1-4}alkoxy;

R^6 represents hydrogen, hydroxy or a C_{1-4}alkyl group optionally substituted by a hydroxy group;

R^7 represents hydrogen, hydroxy, $-(CH_2)_nNR^{11}R^{12}$, $-(CH_2)_nCO_2R^a$, carbocyclyl, C-linked heterocyclyl or heteroaryl, where R^a is as previously defined;

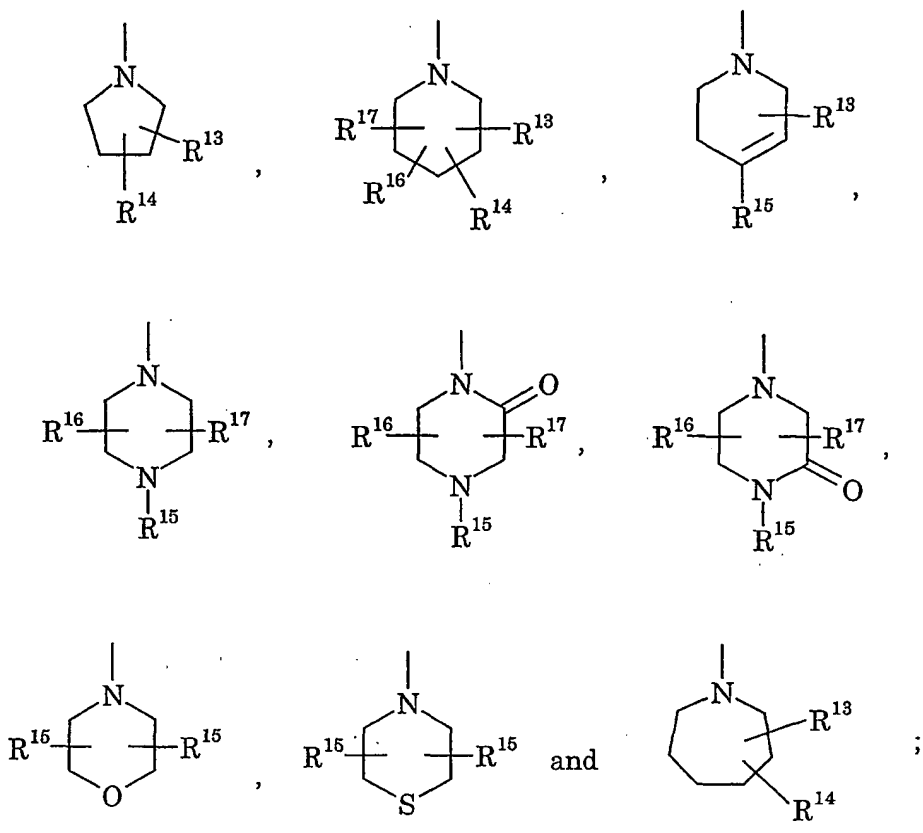
or R^6 and R^7 together represent =O, $=CHCO_2R^a$ or $-O(CH_2)_mO-$, where R^a is as previously defined;

R^8 represents hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkyl substituted by C_{1-4}alkoxy or C_{1-6}alkoxy substituted by C_{1-4}alkoxy;

R^9 represents hydrogen, halogen or hydroxy and R^{10} represents hydrogen; or R^9 and R^{10} both represent fluorine or together represent oxo (=O);

R^{11} and R^{12} each independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl, $CO_2(CH_2)_pNR^aR^b$, $(CH_2)_pNR^aCOR^b$, $(CH_2)_pNR^aCO_2R^b$, $(CH_2)_qCONR^a$aryl or $(CH_2)_qCONR^a$heterocyclyl where R^a and R^b are as previously defined;

or R^{11} and R^{12}, together with the nitrogen atom to which they are attached, represent a ring selected from the group consisting of:

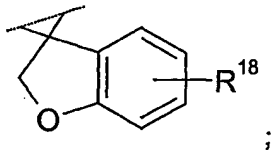


;

R^{13} and R^{14} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, (C_{2-6}alkenyl)aryl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$hétérocyclyl, $(CH_2)_qNR^aR^b$, $O(CH_2)_qC_{3-7}$cycloalkyl, $O(CH_2)_q$aryl, $O(CH_2)_q$heterocyclyl, $O(CH_2)_pNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, when they are attached to the same carbon atom, R^{13} and R^{14} may together represent =O, $=CHCO_2R^a$, $-O(CH_2)_mO-$, $-CH_2O(CH_2)_s-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OCH_2C(CH_3)_2-$, $-CH_2OC(CH_3)_2CH_2-$, $-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-OC(O)CH_2CH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-C(O)OCH_2C(CH_3)_2-$, $-OCH_2(CH_2)_s-$, $-OC(CH_3)_2CH_2CH_2-$, $-OCH_2C(CH_3)_2CH_2-$, $-OCH_2CH_2C(CH_3)_2-$, $-OCH_2CH=CHCH_2-$,

$-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$, $-OCH_2CH_2C(O)CH_2-$, or a group of the formula



;

or, where they are attached to adjacent carbon atoms, R^{13} and R^{14} may together represent $-OCH_2CH_2-$ or $-OCH_2CH(OH)-$, or R^{13} and R^{14} may together form a fused benzene ring;

or, R^{13} and R^{14} together form a C_{1-2}alkylene bridge across the pyrrolidine, piperidine or hexamethyleneimine ring to which they are attached;

R^{15} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, where they are attached to adjacent carbon atoms, R^{15} and R^{16} may together form a fused imidazolyl or triazolyl ring;

R^{16} and R^{17} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl or oxo (=O);

R^{18} represents hydrogen, halogen, hydroxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or fluoroC_{1-4}alkyl;

d is zero, 1, 2 or 3;

n is zero, 1 or 2;

m is 1 or 2;

p is 1, 2, 3 or 4;

q is zero, 1, 2, 3 or 4; and

s is 1, 2 or 3;

or a pharmaceutically acceptable salt or N-oxide thereof.

2. A compound as claimed in Claim 1 wherein R^1 is hydroxy, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{2-6}alkenyloxy,

C_{3-7}cycloalkoxy, C_{3-7}cycloalkylC_{1-4}alkoxy, cyano, NR^aR^b, SR^a, OSO_2R^a, or R^1 together with the group R^2 form a 5-membered saturated ring containing one oxygen atom.

3. A compound as claimed in Claim 1 or Claim 2 wherein R^2 is hydrogen, fluorine or chlorine.

4. A compound as claimed in any one of Claims 1 to 3 wherein R^3 is hydrogen, halogen, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, cyano, NR^aR^b, NR^aCOR^d (where R^d is methyl, methoxy, trifluoromethyl or phenyl), or a 5-membered aromatic heterocyclic group as defined in Claim 1.

5. A compound as claimed in any one of Claims 1 to 4 wherein R^4 is hydrogen.

6. A compound as claimed in any one of Claims 1 to 5 wherein R^5 is hydrogen, fluorine, chlorine or CF_3.

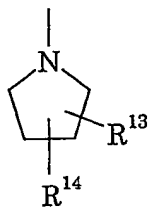
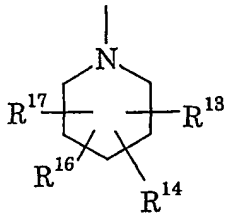
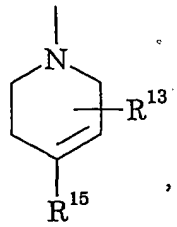
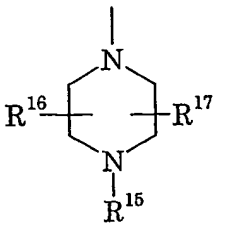
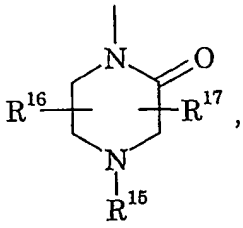
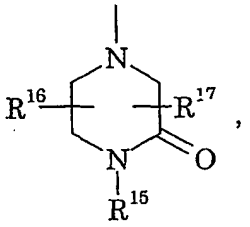
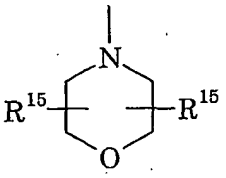
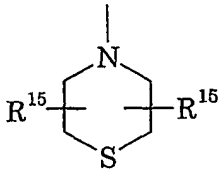
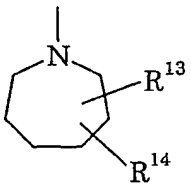
7. A compound as claimed in any one of Claims 1 to 6 wherein R^6 is hydrogen.

8. A compound as claimed in any one of Claims 1 to 7 wherein R^7 is $-(CH_2)_nNR^{11}R^{12}$ or wherein R^6 and R^7 together represent =O or $-O(CH_2)_mO-$ wherein m is 1 or 2.

9. A compound as claimed in Claim 8 wherein R^{11} represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $(CH_2)_pNR^aCO_2R^b$ or $(CH_2)_qCONR^a$aryl;

and R^{12} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl or CO_2C_{1-6}alkyl;

or R^{11} and R^{12} together with the nitrogen atom to which they are attached represent a ring selected from the group consisting of









and


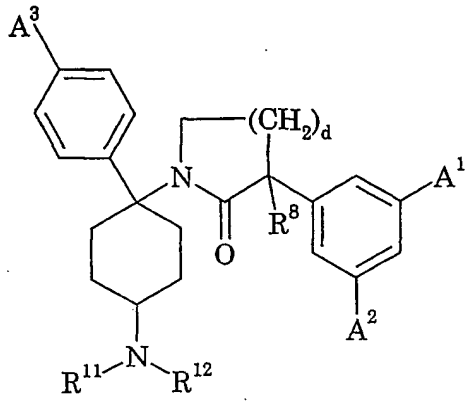
10. A compound as claimed in any one of Claims 1 to 9 wherein R^8 is hydrogen, hydroxy, C_{1-4}alkyl or C_{1-4}alkoxy.

11. A compound as claimed in any one of Claims 1 to 10 wherein R^9 and R^{10} each represent hydrogen.

12. A compound as claimed in any one of Claims 1 to 11 wherein the ring A is a phenyl ring.

13. A compound as claimed in any one of Claims 1 to 10 wherein d is 1 or 2.

14. A compound as claimed in Claim 1 of the formula (Ia):



(Ia)

wherein

A^1 is fluorine or CF_3;

A^2 is fluorine or CF_3;

A^3 is fluorine or hydrogen;

d is 1 or 2; and

R^8, R^{11} and R^{12} are as defined in Claim 1;

or a pharmaceutically acceptable salt or N-oxide thereof.

15. A compound as claimed in any preceding claim for use in therapy.

16. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 14, together with at least one pharmaceutically acceptable carrier or excipient.

17. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to Claim 1.

18. A method for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety, which method comprises administration to a patient in need thereof of a therapeutically effective amount of a compound according to Claim 1.

19. Use of a compound as claimed in any one of Claims 1 to 14 for the manufacture of a medicament for the treatment or prevention of physiological disorders associated with an excess of tachykinins.

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20. Use of a compound as claimed in any one of Claims 1 to 14 for the manufacture of a medicament for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02654

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4025 A61K31/4525 C07D405/08 C07D211/76 C07D207/27
C07D401/08 C07D403/08 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 01 87866 A (ELLIOTT JASON MATTHEW ;HOLLINGWORTH GREGORY JOHN (GB); MERCK SHARP) 22 November 2001 (2001-11-22) abstract examples claims	1-21
A	US 5 776 959 A (FERRENDELLI JAMES A ET AL) 7 July 1998 (1998-07-07) abstract claims	1-21
A	WO 98 03493 A (NEUROGEN CORP) 29 January 1998 (1998-01-29) abstract claims	1-21

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2002	23/08/2002

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/02654

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 18,19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02654

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 0187866 A1	22-11-2001
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